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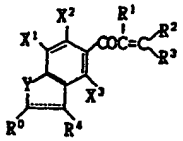
(56) Documents cited
None

(58) Field of search
C2C

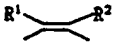
(54) Benzofuran and benzothiophene derivatives

(57) New diuretic antihypertensives, i.e., benzofuran or benzothiophene derivatives have the formula:

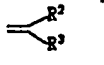
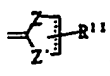
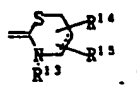


(I)

wherein X^1, X^2, and X^3 are each independently hydrogen, halogen or CH_3; Y is an oxygen or sulfur atom; R^1 is hydrogen, alkyl, alkenyl, aryl, aralkyl or alkoxycarbonyl; R^2 is SR^5, OR^6 or NR^7R^8, wherein R^5 is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or carbamoylmethyl, R^6 is alkyl, R^7 and R^8 are each independently hydrogen, alkyl, alkenyl, cycloalkyl, aryl, furylmethyl or acyl or when R^7 and R^8 are considered together with the adjacent nitrogen atom they may form pyrrolidino, piperidino or morpholino or one of R^7 and R^8 is hydrogen and the other is $-C(O)R^{22}$ where R^{22} is alkyl, substituted alkyl, alkylene or substituted alkylene; R^3 is SR^9 or $S(O)R^{10}$, wherein R^9 is hydrogen, alkyl, alkenyl, alkynyl or aralkyl and R^{10} is alkyl; R^4 is hydrogen or alkyl, R^0 is CHO, $COCH_3$, $COOCH_2COOH$, CN, CH=NOH, COR_{17}, CH_2OR_{18}, $CONR_{19}R_{20}$ or $CH_2OC(O)-CH_2R_{21}$, wherein R_{17} is hydrogen, alkali metal, or alkyl, R_{18} is hydrogen, alkyl or acyl, R_{19} and R^{20} are each independently hydrogen or alkyl or R_{19} andR_{20} may form pyrrolidino together with the adjacent nitrogen atom, and R_{21} is hydrogen or lower alkyl;


may be  ; and,

may be any one of the following;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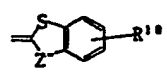

wherein Z is O, S, or NH, Z' is S or N–R_{12}, Z" is S, NH or N–CH_3, R_{11} is hydrogen, alkyl, alkoxy, carbonyl or methylene, R_{12}, R_{13}, R^{14} and R_{16} are each independently hydrogen or alkyl, R_{15} is hydrogen or carbonyl, and the dotted line represents the presence or absence of a double bond.

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SPECIFICATION

Benzofuran and benzothiophene derivatives

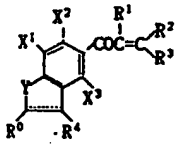
The present invention relates to novel benzofuran and benzothiophene derivatives having antihypertensive, diuretic and uricosuric activities.

All diuretic antihypertensives are classified, by the actions and structures thereof, as diuretic thiazides, loop diuretics, or potassium-sparing diuretics such as antialdosterone-type compounds. The benzofuran- or benzothiophene-derivatives of the present invention can reasonably be classified into the loop diuretics category. The following are representatives of loop diuretic agents which are clinically used or are under research and development.

Ethacrynic acid: Edecril® (Nippon Merck-Banyu),
Chlorthialidone: Hygroton® (Fujisawa Pharmaceutical Co., Ltd./Ciba-Geigy Japan),
Mefruside: Baycaron® (Yositomi Pharmaceutical Ind.)
Furosemide: Lasix® (Hoechst)
Bumetanide: Lunetoron® (Sankyo Co., Ltd)
Tienilic acid, or Ticrynafen: U.S. Patent No. 3,758,506 (C.E.R.P.H.A.),
Indacrinone and the derivatives: Japanese Unexamined Patent Publication Nos. 57–163338, 57–163339, 57–176920, 57–176968, 57–209246 (Merck),
Benzenesulfonamide derivatives substituted at 2, 3 and 4 positions: JPN Unexam. Pub. No. 58–124758 (Fujisawa Pharmaceutical Co., Ltd.),
5-Acyl-substituted-2,3-dihydrobenzofuran derivatives: JPN Unexam. Pub. No. 52–10261 (Merck).

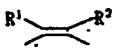
The compounds of this invention are also acyl-substituted-2, 3-dihydrobenzofuran derivatives in their essential structure, but are different in their partial structure to those referred to above.

This invention thus provides new diuretic compounds which can, for example, be administered orally at a daily-dosage of 0.5–200 mg, preferably 1–100 mg, or parenterally at e.g., 0.01–50 mg. preferably 0.1–20 mg, and which have the following formula (I):



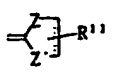
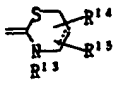
(I)

wherein X^1, X^2, and X^3 are each independently hydrogen, halogen or CH_3; Y is an oxygen or sulfur atom; R^1 is hydrogen, alkyl, akenyl, aryl, aralkyl or alkoxycarbonyl; R^2 is SR^5, OR^6 or NR^7R^8, wherein R^5 is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or carbamoylmethl, R^6 is alkyl, R^7 and R^8 are each independently hydrogen, alkyl, alkenyl, cycloalkyl, aryl, furylmethyl or acyl or when R^7 and R^8 are considered together ewith the adjacent nitrogen atom they may form pyrrolidino, piperidino or morpholino or one of R^7 and R^8 is hydrogen and the other is $-C(O)R^{22}$ where R^{22} is alkyl, substituted alkyl, alkylene or substituted alkylene; R^3 is SR^9 or $S(O)RR^{10}$, wherein R^9 is hydrogen, alkyl, alkenyl, alkynyl or aralkyl and R^{10} is alkyl; R^4 is hydrogen or alkyl, R^0 is CHO, $COCH_3$, $COOCH_2COOH$, CN, CH=NOH, $COOR^{17}$, CH_2OR^{18}, $CONR^{19}R^{20}$ or $CH_2OC(O)-CH_2R^{21}$, wherein R^{17} is hydrogen, alkali metal, or alkyl, R^{18} is hydrogen, alkyl or acyl, R^{19} and R^{20} are each independently hydrogen or alkyl or R^{19} and R^{20} may form pyrrolidino together with the adjacent nitrogen atom, and R^{21} is hydrogen or lower alkyl;



may be  ; and,

may be any one of the following;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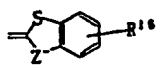
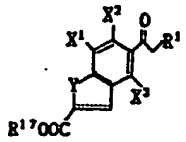


wherein Z is O, S, or NH, Z' is S or N–R^{12}, Z" is S, NH or N–CH_3, R^{11} is hydrogen, alkyl, alkoxy, carbonyl or methylene, R^{12}, R^{13}, R^{14} and R^{16} are each independently hydrogen or alkyl, R^{15} is hydrogen or carbonyl, and the dotted line represents the presence or absence of a double bond. Therapeutically acceptable salts of the compounds of the invention are included within the scope of the invention.

Compounds of the formula (I) can be prepared from benzofuran or benzothiophene derivatives as starting materials having the following formula (III):



(I)

wherein X^1, X^2, X^3, Y, R^1 and R^{17} each has the same meaning as above, according to the processes explained in the reaction schemes given later. Each symbol used in the reaction schemes has the same meaning as above.

Abbreviations used in this specification are listed as follows:

DMA	Dimethylacetamide
DME	Dimethoxyethane
DCC	1,3-Dicyclohexylcarbodiimide
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
p-TsOH	para-Toluenesulfonic acid
Me	Methyl
Et	Ethyl
MeOH	Methanol
EtOH	Ethanol
Et_2O	Diethyl ether
ϕ	Phenyl
qu.	Quantitatively

Compounds of this invention have anti-hypertensive and diuretic activites and can be used as diuretic antihypertensives in the treatment or prophylaxis of essential or renal hypertension, nephredema, cardiac or hepatic edema, gestosis or like diseases.

The compounds of this invention may be administered orally or parenterally (intravenously or intramuscularly) in a suitable form, e.g. such as tablets, granules, fine granules, powders, capsules, injections or like formulations. They can be administered orally in a single or divided doses of 0.5–200 mg a day, preferably 1–100 mg, or parenterally at a dosage of 0.01–50 mg, preferably 0.1–20 mg.

In the formula (I), "alkyl" includes straight or branched chain C_1–C_5 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, s-butyl, isobutyl, pentyl, isopentyl, or the like. "Alkenyl" includes C_2–C_5 alkenyl such as vinyl, 1-propenyl, 2-propenyl, 3-butenyl, 1,4-butadienyl, 3-pentenyl, and the like. "Aryl" includes C_5–C_{12} aryl such as phenyl, naphthyl and the like. "Aralkyl" includes C_7–C_9 aralkyl for example, benzyl, phenethyl, and the like. "Alkoxycarbonyl" includes C_2–C_5 alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, and the like. "Alkynyl" includes C_2–C_5 alkynyl such as ethynyl, 2-propynyl, and the like. "Cycloalkyl" includes C_3–C_7 cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. "Acyl" includes C_1–C_5 alkanoyl (e.g. formyl, acetyl, propionyl, butyryl or valeryl) and benzoyl. "Substituted alkylene" includes C_2–C_4 alkylene which may be substituted and "alkylene" includes C_2–C_4 alkylene such as methylene, ethylene, trimethylene, tetramethylene, and the like. "Halogen", which may be represented by X^1, X^2 or X^3, includes fluorine, chlorine, bromine and iodine.

Most of the starting materials which are used in the Examples which are given below are disclosed in U.S. Patent No. 3,751,436 or J. Med.Chem. 24(7), 865–873, 1981, or can readily be prepared from such materials.

The compounds of the present invention can be prepared by a process comprising effecting the desired step(s) in accordance with any of the following reaction schemes. Thus, multi-stage and single-stage processes are included in the invention.

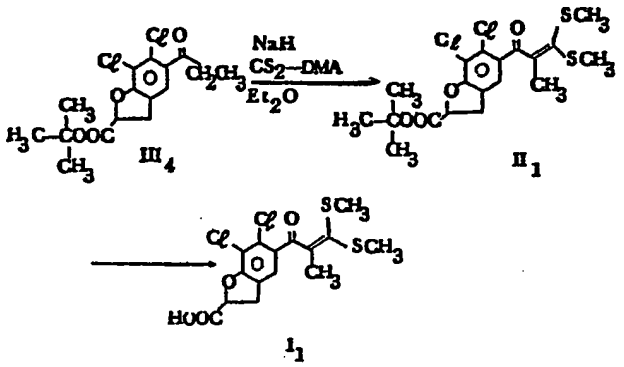
The invention also provides a pharmaceutical or veterinary formulation comprising a compound of the invention or a salt of the invention, in either case formulated for pharmaceutical or veterinary use, respectively. Such formulations may be in unit dosage form and/or include an acceptable diluent, carrier or excipient. Such formulations may be made by standard means and using materials known in the art in accordance with normal practice.

The invention further provides a method of making a medicament for producing an antihypertensive, diuretic or uricosuric effect, which method comprises formulating a compound of the invention or a salt of the invention for such purpose.

The following Examples are provided to illustrate this invention in more detail.

Example 1

Preparation of 6,7-dichloro-5-[2-methyl-3,3-bis(methylthio)-propanoyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid I_1



To a suspension of 2.03 g (55.5 mmol) of 65.6% sodium hydride in 30 ml of dry ether is, under nitrogen flow while being stirred, added a solution of 8.0 g (23.3 mmol) of t-butyl 6,7-dichloro-5-propyonyl-2,3-dihydro-1-benzofuran-2-caboxylate III_4, 5.3 g (69.6 mmol) of carbon disulfide and 9.9 g (69.6 mmol) of iodomethane in 190 ml of dry ether, and then 4.8 ml of N,N-dimethylacetamide and the resulting mixture is allowed to react at room temperature for 72 hours. The reaction mixture is poured into ice-cold water and extracted three times with benzene. The benzene layers are combined, washed with water (four times), dried over magnesium sulfate and evaporated to give 13.2 g of a residue. This is chromatographed on a column of 160 g of silica gel (by Merck 70–230 mesh) with n-hexane/benzene (7/3) (F-1, 2 L), n-hexane/benzene (65/35) (F-2, 2 L), n-hexane/benzene (3/2) (F-3, 2 L), n-hexane/benzene (55/45) (F-4, 1 L), n-hexane/benzene (1/1) (F-5, 0.5 L), n-hexane/benzene (3/7) (F-6, 1 L), n-hexane/benzene (1/4) (F-7, 0.8 L), and benzene (F-8, 1 L) in order. From the last three fractions, i.e. F-6, F-7, and F-8 is obtained 9.4 g of compound II_1, as an oil, yield 90.3%.

IR νmax ($CHCl_3$): 1740 (C(O)–O–C–$(CH_3)_3$), 1640 cm $^{-1}$.

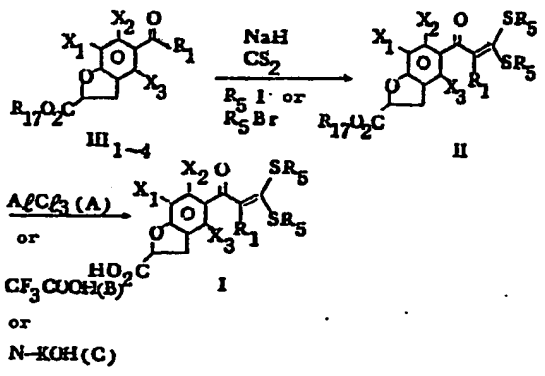
NMR δppm ($CDCl_3$): 1.50 (9H, s), 2.23 (3H, s), 2.00 (3H, s), 2.35 (3H, s), 3.20–3.93 (2H, m), 5.10–5.45 (1H, m), 7.37–7.42 (1H, m).

To a solution of 7.7 g (17.1 mmol) of the compound II_1 in 80 ml of dry dichloromethane is added 2.7 g (20.2 mmol) of anhydrous aluminium chloride (powder) under ice-cooling while being stirred and the mixture is allowed to react for an hour and then for additional 2.5 hours at room temperature.

The reaction mixture is poured into ice-cold water, then combined with 6 ml of 10% hydrochloric acid, and extracted three times with ether. The ether layers are combined, washed with water, dried over magnesium sulfate and evaporated to give 6.8 g of a residue. The residue is treated with a mixture of n-hexane-isopropyl ether to give crystals, mp. 124–128°C, which are recrystallized from isopropyl ether to give 5.6 g of yellowish white crystals, yield 83.1% mp. 131–132°C.

Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_4S_2$
: C 45.80 H 3.59, Cl 18.03, S 16.31,
Found (%) : C 45.52, H 3.63, Cl 17.91, S 16.25.
IR νmax (Nujol) : 2630, 1724, 1710, 1648, 1605 cm $^{-1}$.

Example 2-15



III 1-4 II I

The compounds (I_{2-15}) are prepared in the same manner as in Example 1, whose physical constants and reaction conditions are shown in the following Table 1 (Nos. 1 and 2).

Table 1 (No. 1)

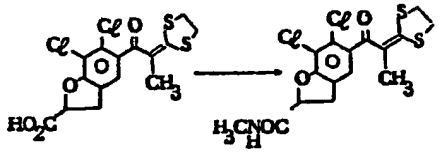
Example No.	III R_{17}	III R_1	III X_1	III X_2	III X_3	Amount Used (mmol) III	65.6% NaH	CS_2	R_5I or Br	Solvent in Et_2O DMA or DME	Temp.	Time	II R_5	II Yield (%)	II NMR : δ $CDCl_3$ ppm
2	tBu	CH_3	Cℓ	Cℓ	H	2.5 (7.2)	0.64 (17.5)	1.66 (21.8)	CH_2ClI 3.70 (21.0)	Ether 30 1.5	25 ~ 27℃	72	$(CH_3)_2CH$-	7.7	100(6H,d)130(6H,d)150(9H,s) 227(3H,s)307~393(4H,m) 510~540(1H,m)738(1H)
3	〃	〃	〃	〃	〃	1.5 (4.3)	0.38 (10.4)	0.99 (13.0)	$BrCH_2Br$ 2.45 (13.0)	〃 25 0.9	〃	148	$-(CH_2)_2-$	32.9	140(9H,s)200(3H,s)307~370(6H, m)503~537(1H,m)692(1H)
4	〃	〃	〃	〃	〃	3.0 (8.7)	0.76 (20.8)	2.0 (26.3)	$BrCH_2Br$ 5.30 (28.3)	〃 30 1.8	〃	96	$-(CH_2)_3-$	7.7	150(9H,s)247~200(5H,m) 273~393(6H,m)505~543(1H,m) 698~708(1H)
5	C_2H_5	〃	〃	〃	〃	4.0 (9.9)	1.10 (30.1)	2.90 (38.1)	ϕCH_2I 6.50 (38.0)	〃 40 2.6	〃	48	ϕCH_2-	34.7	130(t,3H)205(s,3H)317~356(2H,m) 380(s,2H)403(2H,s)429(2H,q)517~ 550(1H,m)687~747(1H)
6	tBu	H	〃	〃	〃	4.2 (9.27)	1.12 (30.0)	2.90 (38.1)	CH_3I 5.40 (38.2)	〃 70 2.6	〃	72	CH_3-	70.7	~707
7	〃	〃	〃	〃	〃	2.4 (7.2)	0.64 (17.4)	1.68 (22.1)	EtI 3.40 (21.8)	〃 36 1.5	〃	72	C_2H_5-	81.8	137(6H,t)148(9H,s)277(6H,m) 502~537(1H,m)720(1H)
8	C_2H_5	φ	〃	〃	〃	1.8 (4.7)	0.42 (11.5)	1.06 (14.2)	CH_3I 2.02 (14.2)	DME 16 0.90	〃	24	CH_3-	72.1	127(3H,t)220(6H,s)333~363(2H,m) 422(q,2H)513~542(1H,m) 712~748(6H)
9	〃	ϕCH_2	〃	〃	〃	0.3 (0.8)	0.07 (1.8)	0.18 (2.3)	CH_3I 0.323 (2.3)	〃 6 0.16	〃	72	CH_3-	24.0	128(3H,t)197(3H,s)238(s,3H) 307~348(2H,m)375(2H,s)425(2H,q) 512~540(1H,m)658(1H)720(6H)
10	〃	NO_2 (o)	〃	〃	〃	1.0 (2.4)	0.32 (8.0)	0.56 (7.4)	1.04 (7.3)	〃 7 0.5	〃	24	CH_3-	84.0	130(3H,t)222(3H,s)227(3H,s)313~ 392(2H,m)425(2H,q)520~547(1H,m) 740(1H)757~817(4H,d-d)
11		CH_3	H	Cℓ	H	0.99 (3.5)	0.29 (7.7)	0.67 (8.8)	1.24 (8.8)	Ether 19 0.72	〃	72	CH_3-	17.3	130(t,3H)200(3H,s)221(3H,s)234(3H,s)317~373(2H,m)426(2H,q)525(1H,d-d)687(1H,s)752(1H,m)
12		CH_3	H	H	Cℓ	1.20 (4.2)	0.34 (9.3)	0.81 (10.9)	1.51 (10.9)	〃 23 0.9	〃	216	CH_3	17.6	196(3H,s)220(3H,s)233(3H,s) 130(3H,t)320~380(2H,m)426(q,2H) 525(1H,d-d)677(1H,d)753(1H)
13	C_2H_5	CH_3	H	H	H	2.52 (9.02)	0.82 (22.3)	1.93 (25.4)	3.62 (25.4)	〃 54 2.2	〃	72	CH_3	8.4	130(t,3H)210(3H,s)217(3H,s)235(3H,s)320~377(2H,m)426(2H,q)525(d-d,1H)717~778(m,2H)690(1H)
14	C_2H_5	CH_3	CH_3	Cℓ	H	1.50 (5.11)	0.41 (11.1)	0.96 (12.6)	1.80 (12.6)	〃 27 1.1	〃	96	CH_3	8.8	128(3H,t)197(3H,t)221(3H,s)228(s,3H)233(9H,s)321~375(2H,m)425(2H,q)529(1H,d-d)736(1H,s)
15	tBu	CH_3	CH_3	CH_3	H	0.61 (2.1)	0.165 (4.6)	0.40 (5.3)	0.75 (5.3)	HMF 10 0.4	〃	72	CH_3	37.0	148(9H,s)226(3H,s)234(3H,s) (244(S)250(S)H)310~370(2H,m) 508(1H,d-d)936(1H,s)2716(1H)

Table 1 (No. 2)

Example No.	Amount Used: H·Y (mmol)	Amount Used: AlCl$_3$(A) CF$_3$CO$_2$H(B) H-KOH(C) (g)	(%)	Recrystal From	m.p. °C	Molecular Formula	C H Cl S N	I R	N¹ M R
2	0.23	B	83.3	hexane/ isopropyl ether	121~ 122	$C_{19}H_{22}Cl_2O_4S_2$	50.78 4.93 15.78 14.27 50.70 4.78 15.94 14.28	2030.2540. 1715.1661.1611	
3	0.64	B	88.4	acetone	231~ 232(d)	$C_{15}H_{12}Cl_2O_4S_2$	46.04 3.09 18.12 16.39 4600 3.05 17.86 16.12	2650.2560.1753 1710.1616.1603	
4	0.55	B	82.8	acetone	221~ 222	$C_{16}H_{14}Cl_2S_2O_4$	47.41 3.48 17.50 15.82 47.15. 3.60 17.39 15.62	2680.2585.2490 1750.1608.1570	
5	0.70	C	49.5	ether/ isopropyl ether	128~ 130	$C_{27}H_{22}Cl_2O_4S_2$	59.46 4.07 13.00 11.76 59.55 3.94 13.03 11.68	2720.2645.2560 1737.1712.1647. 1611	
6	8.80	A	83.4	dioxane/ ether	258~ 260(d)	$C_{14}H_{12}Cl_2O_4S_2$	44.33 3.19 18.70 16.91 44.37 3.27 18.65 16.89	2700.2570.2480 1745.1607.1560	(2.40(S)2.53(S)(6H)) 3.10~3.93 (2H,m) 5.31~5.58 (1H,m) 6.40 (1H,S) 7.35 (1H,S)
7	2.60	A	62.1	acetone	175~ 177	$C_{16}H_{16}Cl_2O_4S_2 \cdot 1/4H_2O$	46.66 4.02 17.22 15.57 46.60 3.94 17.40 15.67	2600.2560.2470 1750.1611.1553	(1.32;1.35 6H (×2) 2.87~3.30 (m, 4H) 3.47~3.80 (m, 2H) 7.30 (1H, S) 5.33~6.00 (2H, m D$_2$O 1H) 6.52 (1H, S)
8	1.60	C	55.1	ether/ isopropyl ether	103~ 105	$C_{20}H_{16}Cl_2O_4S_2$	52.76 3.54 15.57 14.08 52.60 3.76 15.61 13.86	2640.2540.1735 1710.1662.1605	
9	0.091 (0.2)	C	84.7	hexane/ isopropyl ether	138~ 139	$C_{21}H_{18}Cl_2O_4S_2$	53.73 3.81 15.11 13.66 53.67 4.02 15.25 13.63	2660.2580.1740 1713.1653.1603	
10	0.165 (0.3)	C	64.1	ether/ isopropyl ether	134~ 136	$C_{20}H_{15}Cl_2NO_6S_2$	48.00 3.02 14.17 12.82 2.80 47.93 3.01 13.92 12.65 2.80	3460~3360 1770.1739.1682 1605.1614	
11	0.23	C	38.0	isopropyl ether	129~ 130	$C_{15}H_{15}ClO_4S_2$	50.20 4.21 9.88 17.87 50.30 4.13 9.99 17.85	3300~2400.1714 1665.1618.1580	1.98 (S, 3H) 2.18 (3H, S) 2.37 (3H, S) 3.25~3.84 (2H, m) 5.42 (1H, d-d) 6.91 (1H, S) 7.57 (1H)
12	0.28	C	84.1	hexane/ isopropyl ether	96~ 97	$C_{15}H_{15}ClO_4S_2$	50.06 4.17 9.68 17.55	3000~2000.1740 1652.1600.1590	1.97 (3H, S) 2.18 (3H, S) 2.36 (3H, S) 3.26~3.85 (2H, m) 6.50 (1H, S) 6.84 (1H, d) 7.55 (1H)
13	0.30	C	65.3	isopropyl ether	137~ 138	$C_{15}H_{16}O_4S_2$	55.54 4.97 19.78 55.24 4.94 19.72	3400~2000 1737.1642.1602 1438	2.07 (S, 6H) 2.34 (3H, S) 3.15~3.80 (2H, m) 5.35 (1H, d-d) 6.94 (1H, d) 7.05~7.20 (2H, m)
14	0.17	C	51.3	hexane/ isopropyl ether	129~ 130	$C_{16}H_{17}ClO_4S_2$	51.64 4.59 9.50 17.19 51.45 4.52 9.61 17.12	3300~2400 1748.1645.1592	
15	0.35	A	79.7	ethanol	246~ 248	$C_{16}H_{18}O_4S_2$	56.78 5.36 18.95 56.49 5.22 18.74	3200~2200 1746.1562	

Example 16

6,7-Dichloro-5-[2-(1,3-dithiolan-2-ylidene)-propyonyl]-2,3-dihydro-1-benzofuran-2-N-methylformamide



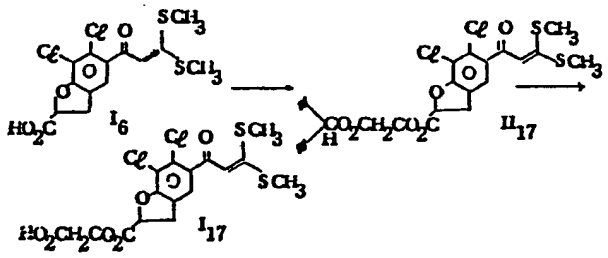
I_3 I_{16}

In 5 ml of dichloromethane, 0.250 g (0.6 mmol) of the compound (I_3), 0.138 g (0.7 mmol) of 1,3-dicyclohexyl carbodiimide (D.C.C.) and a large excess amount of methylamine are allowed to react at room temperature for 20 hours. The reaction product is purified by chromatography on a Lober column (Type B) with a mixture of chloroform-benzene-ethyl acetate (3/1/1) to give 0.21 g of the compound (I_{15}), yield 46.5%, mp. 230–233°C (dec.), which is recrystallized from ethyl acetate to give 0.091 g of grayish crystals, yield 34.9%, mp. 232–234°C (dec.).

Anal. Calcd. (%) for $C_{15}H_{15}Cl_2NO_3S_2$
: C 47.53 H 3.74, Cl 17.54, N 3.46, S 15.86,
Found (%) : C 47.54, H 3.69, Cl 17.81, N 3.55, S 15.90.
IR νmax(Nujol) : 3315, 3310, 1654, 1615, 1603 cm $^{-1}$.
NMR δppm ($CDCl_3$) : 2.00(3H,s), 2.88(3H,d), 3.22–3.73(6H,m), 5.17–5.45(1H,m), 6.60(1H,br), 6.97(1H)

Example 17

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxyacetic acid



To 0.44 g (1.2 mmol) of the compound I_6 (prepared from Example 6) are added 0.263 g (1.3 mmol) of 1,3-dichlorohexylcarbodiimide and 5 ml of dry dioxane, and the mixture is stirred at room temperature for 2 hours. The mixture is combined with 0.337 g (1.4 mmol) of diphenylmethyl glycolate and allowed to react for further 72 hours. The reaction product is purified by liquid chromatography on a Lober column (Type B) with a mixture of benzene-ethyl acetate (10/1) to give 0.345 g of the compound II_{17}, yield 49.3%

NMR δppm ($CDCl_3$): 2.47 (3H, s), 2.53 (3H, s), 3.25–3.75 (2H, m), 4.83 (2H, s), 5.30–5.57 (1H, m), 6.43(1H, s), 6.92 (1H, s), 7.22–7.40 (11H, m).

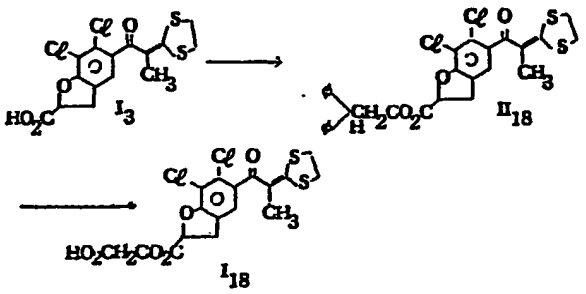
To 0.34 g (0.6 mmol) of the compound II_{17} are added 0.68 ml of anisole and 0.68 ml of trifluoroacetic acid. The mixture is allowed to react at room temperature for 5/6 hours while being stirred. The solvent is removed by evaporation and the residue is treated with n-hexane to give 0.243 g of the compound I_{17}, yield 98.8%, mp. 170–173°C. This is recrystallized from ether-acetone to give 0.22 g of grayish white crystals, yield 89.4%, mp. 172–174°C.

Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_6S_2$
: C 43.94 H 3.23, Cl 16.22, S 14.66,
Found (%) : C 43.78, H 3.38, Cl 15.98, S 14.37.
IR νmax(Nujol) : 3090, 1765, 1742, 1615, 1590 cm $^{-1}$.

Example 18

6,7-Dichloro-5-(2-methyl-1,3-dithiolan-2-ylpropyonyl)-2,3-dihydro-1-benzofuran-2-carboxyacetic

acid



To 0.50 g (1.3 mmol) of the compound I_3 (prepared in Example 1) are added 0.277 g (1.3 mmol) of 1,3-dicyclohexylcarbodiimido, 0.60 g (2.5 mmol) of diphenylmethyl glycolate and 5 ml of dioxane, and the mixture is allowed to react and then worked up in the same manner as in Example 17 to give 0.415 g of the compound II_{18}, yield 52.8%.

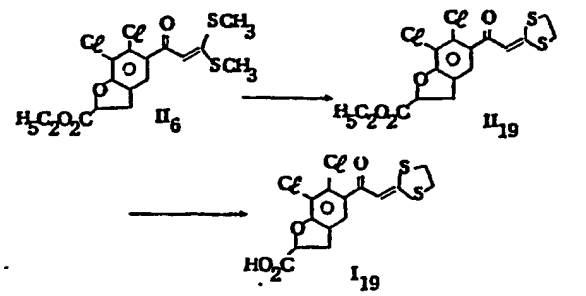
NMR δppm ($CDCL_3$): 1.95 (3H, s), 3.07–3.67 (6H, m), 4.73 (2H, s), 5.18–5.47 (1H, m), [6.83(s), 6.80 (s) 2H], 7.23 (10H).

A mixture of 0.40 g (0.6 mmol) of the compound II_{18} with 0.8 ml of anisole and 0.8 ml of trifluoroacetic acid is treated in the same manner as in Example 1 to give 0.292g of the compound I_{18}, yield 100%, mp. 200–203°C, which is recrystallized from ethyl acetate to give 0.260 g of the grayish white crystals, yield 89.0%, mp. 202–204°C.

Anal. Calcd.(%) for $C_{17}H_{14}CL_2O_5S_2$
: C 45.44 H 3.14, Cl 15.78, S 14.27,
Found (%) : C 45.26, H 3.36, Cl 15.59, S 14.09.
IR : νmax(Nujol) 3040, 2670, 2570, 1768, 1740, 1715, 1612, 1602.

Example 19

5,7-Dichoro-5-[2-(1,3-dithiolan-2-ylidene)acetyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid.



The compound II_6 (prepared in Example 6) (0.60 g, 1.5 mmol) is allowed to react with 0.208g (2.2 mmol) of ethanedithiol in 10 ml of toluene for 24 hours on an oil bath (140–145°C) while being stirred. The reaction product is chromatographed on a Lober column (Type B) with a n-hexane/ethyl acetate (7/3) mixture to give 0.288 g of the compound II_{19} (oil), yield 48.0%.

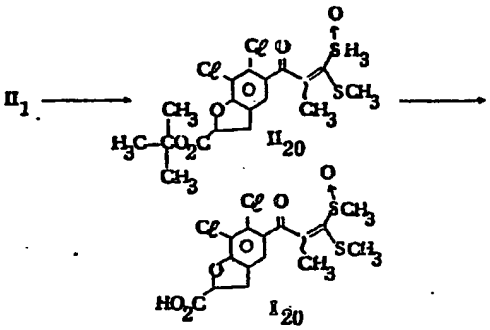
NMR δppm ($CDCl_3$): 1.30 (3H, t), 3.13–3.77 (6H, m), 4.25 (2H, q), 5.17–5.55 (1H, m), 6.95(1H, s), 7.17–7.40 (1H).

To 0.52 g (1.3 mmol) of the compound II_{19} are added 2 ml of ethanol, 2 ml of dioxane and 2 ml (2 mmol) of 1 N sodium hydroxide, and the mixture is allowed to react at room temperature for 30 minutes to give 0.487 g of the compound I_{19}, yield 100%, mp, 215–218°C. This is recrystallized from acetone to give 0.42 g of grayish white crystals, yield 86.8%, mp. 217–218°C.

Anal. Calcd. (%) for $C_{14}H_{10}Cl_2O_4S_2$
: C 44.57 H 2.67, Cl 18.80, S 17.00,
Found (%) : C 44.38, H 2.62, Cl 19.03, S 16.77.
IR νmax (Nujol) : 2720, 2560, 2470, 1743, 1610. 1580 cm $^{-1}$.

Example 20

6,7-Dichloro-5-[2-methyl-3,3-bis(methylthio)propenoyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid monosulfoxide



To a solution of 0.67 g (1.5 mmol) of the compound II_1 (prepared in Example 1) in 11.2 ml of dry dichloromethane is added in small portions 0.26 g (1.5 mmol) of m-chloroperbenzoic acid in a 40 minute period under flowing nitrogen while being stirred at an internal temperature of −7 to −5°C. The resulting mixture is allowed to react at the same temperature for 15 minutes and then at room temperature for 40 minutes. The product is chromatographed on a Lober (Type B) column with a chloroform/benzene/ethyl acetate (3/1/1) mixture to give 0.20 g of the compound II_{20} as an oil, yield 28.8%.

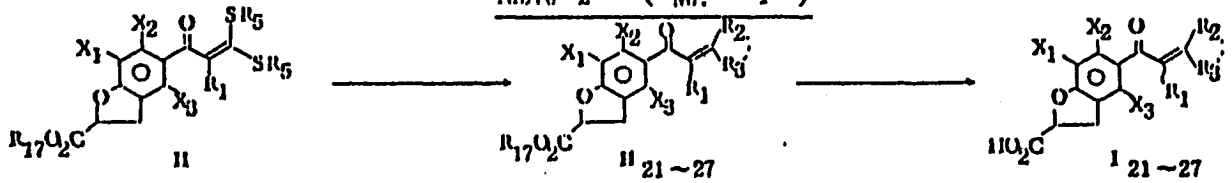
NMR δppm ($CDCl_3$): 1.50 (9H, s), 2.20 (3H, s), 2.33 (3H, s), 2.70 (3H, s), 3.10–3.93 (2H, m), 5.13–5.43 (1H, m), 7.60 (1H).

In the same manner as in Example 1, 0.20 g (0.4 mmol) of the compound II_{20} is treated with trifluoroacetic acid and the ether-soluble matter is recrystallized from ethyl acetate to give 0.55 g of grayish white crystals, yield 31.1%, mp. 197–199°C (dec.).

Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_5S_2$
: C 44.01 H 3.45, Cl 17.33, S 15.67,
Found (%) : C 44.02, H 3.54, Cl 17.35, S 15.76.
IR : νmax(Nujol) 2600, 2470, 1720, 1670, 1605.

Examples 21–27

Compound I_{21-27} and their intermediates II_{21-27} are prepared in the same manner as in Example 19 or 20, whose physical constants and reaction conditions are shown in the following Table 2 (Nos. 1 and 2).



II　　II 21～27　　I 21～27

Table 2 (No. 1)

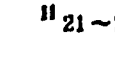
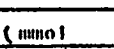
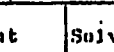
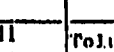
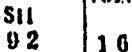
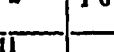
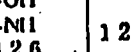
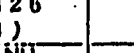
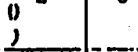
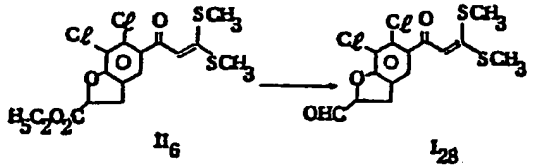
Example Nos.	II R_{17}	R_1	R_5	X_1	X_2	X_3	Amount Used/g (mmol) II	Reagent	Solvent	Temp.	Time	$\left(\begin{smallmatrix}R_2\\R_3\end{smallmatrix}\right)=$	Yield (%)	NMR
21	tBu	CH_3	CH_3	Cℓ	Cℓ	H	1.60 (3.6)	0.292 (3.7)	Toluene 16 ml	140～145°	24		42.9	1.50(9H,S) 1.83(3H,S) 3.10～3.90(4H,m) 4.53(2H,t) 5.05～5.40(m,1H) 6.88～7.00(1H)
22	〃	〃	〃	〃	〃	〃	2.00 (4.5)	 0.326 (5.3)	12	〃	28		16.8	1.47(9H,S) 1.62(3H,S) 3.07～3.63(2H,m) 3.85(2H,t) 4.55(2H,t) 5.05～5.35(1H,m) 6.85～6.98(1H) 10.4～9.00(1H)
23	〃	〃	〃	〃	〃	〃	1.20 (2.7)	 0.20 (3.3)	6	〃	20		35.2	1.45(12H,S) 3.03～3.97(6H,m) 5.20～5.65(1H,m) 6.98(1H) 7.18(br,1H) 9.70(br,1H) DMSO
24	CH_3	〃	〃	〃	〃	〃	2.0 (4.9)	HCl gas	MeOH 20 ml	−50°	7	CH_3S 	8.3	1.83(3H,S) 2.13(6H,S) 3.17～3.76(5H,m) 3.83(3H,S) 5.18～5.55(1H,m) 6.80～6.92(9H)
25	〃	〃	〃	〃	〃	〃	0.50 (1.2)	 0.5 (4.5)	Toluene 5	140～145°	12	CH_3S 	72.9	[1.82(S)2.30(S)3H][2.22(S)2.28(S)3H]3.08～3.73(2H,m)[3.77,3.80(3H)]5.12～5.52(1H,m)7.07～7.47(6H,m)
26	CH_3	〃	〃	〃	〃	〃	0.65 (1.6)	 0.52 (3.3)	Toluene 6.5	140～145°	20		15.4	2.02(3H,S) 2.40(3H,S) 3.23～3.73(2H,m) 3.82(3H,S) 5.22～5.48(1H,m) 6.82～7.58(4H)
27	C_2H_5	H	〃	〃	〃	〃	0.23 (0.6)	HCℓ gas	EtOH 20	25°	3.5	CH_3S 	69.9	[1.07(t)1.12(t)3H]2.35(3H,S) 3.13～3.17(2H,m) 4.00(q−q,2H) 4.27(q,2H) 1.32(t,3H) 5.13～5.48(1H,m) 5.73(1H,S) 6.87～7.00(4H)

Table 2 (No. 2)

Example No.	Amount Used g (mmol) II	CF_3CO_2H (A) ROH (B)	Temp	Time	Recrystal from	m.p.	Yield %	molecular formula	Elementary Analysis (%) Calcd. / Found C	H	Cℓ	N	S	IR
21	0.64 (1.5)	A	25	0.5	Dioxane/ ether	253~255(d)	80.3	$C_{15}H_{12}Cℓ_2O_5S$	48.01 / 47.99	3.22 / 3.44	18.90 / 18.84		8.55 / 8.40	2685,2560,2480,1740, 1610,1570,
22	0.42 (1.0)	A	〃	1	—	241~242(d)	55.9	$C_{15}H_{13}Cℓ_2NO_5$	50.29 / 49.99	3.66 / 3.76	19.80 / 20.07	3.91 / 3.88		3295,2480,1730,1620, 1610
23	0.58 (1.4)	A	〃	2/3	Acetone	273~276(d)	73.9	$C_{15}H_{14}Cℓ_2N_2O_4$	50.44 / 50.49	3.95 / 4.08	19.85 / 19.78	7.84 / 7.59		3465,3330,2460,1730, 1600
24	0.15 (0.4)	B	〃	1	Ether/ Hexane	105~107	34.5	$C_{15}H_{14}Cℓ_2O_5S$	47.75 / 47.79	3.74 / 4.04	18.80 / 18.71		8.50 / 8.30	2720~2370,1682(sh1720, 1710)1608
25	0.42 (0.9)	B	〃	1	Isopropyl ether	76~78	29.5	$C_{20}H_{16}Cℓ_2O_4S_2$	52.75 / 52.91	3.54 / 3.70	15.57 / 15.31		14.08 / 14.00	2690,2590,1743,1714, 1655,1605
26	0.15 (0.3)	B	〃	3	Acetone	215~217(d)	66.0	$C_{20}H_{14}Cℓ_2O_4S_2 \cdot \frac{1}{2}H_2O$	51.95 / 52.25	3.16 / 3.28	15.34 / 15.29		13.87 / 13.65	3380,2720,2620,2540, 1708,1747,1605,1594
27	0.395 (1.0)	B	〃	1	Ether/ Petroleum ether	135~136	67.9	$C_{15}H_{14}Cℓ_2O_5S$	47.75 / 47.65	3.74 / 3.75	18.80 / 18.98		8.50 / 8.29	3230,1702,1693,1610

Example 28

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxaldehyde



II_6 I_{28}

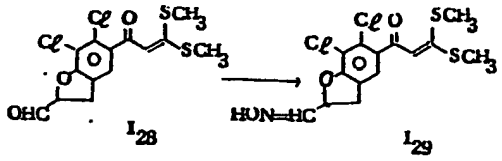
To a cooled solution (−78°C) of 0.55 g of the compound II_6 (prepared in Example 6) in 6 ml of dry tetrahydrofuran (THF) is added 0.39 ml of a solution of 70% sodium bis(2-methoxyethoxy)aluminium hydride in toluene in 10 minutes while being stirred under nitrogen atmosphere. The mixture is allowed to react for 30 minutes. The reaction mixture is combined with 10% hydrochloric acid and extracted with benzene (3 times). The benzene layer is washed with water, dried over dry magnesium sulfate and evaporated to give a residue, which is chromatographed on a Lober column (Type B) with chloroform/benzene/ethyl acetate (3/1/1) to give 0.40 g of the compound I_{28}, yield 81.6%, mp. 160–163°C.

This is recrystallized from acetone to give 0.350 g of grayish white crystals, yield 71.4%, mp. 163–165°C.

Anal. Calcd. (%) for $C_{14}H_{12}Cl_2O_3S_2$
: C 46.28 H 3.33, Cl 19.52, S 17.65,
Found (%) : C 46.05, H 3.54, Cl 19.59, S 17.49.
IR νmax(Nujol) : 2710, 1733, 1625, 1603 cm $^{-1}$.
NMR δppm (DMSO d_6) : 2.50 (s), 2.55 (s), 5.43–5.73 (1H, m), 3.37–3.68 (2H, m), 6.43 (1H,s), 7.42 (1H), 9.70 (1H, s).

Example 29

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxaldoxime



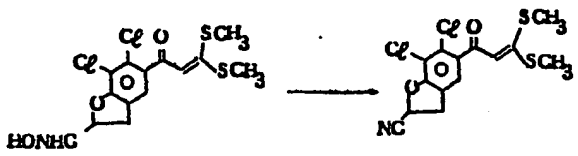
I_{28} I_{29}

A mixture of 0.18 g (0.5 mmol) of the compound I_{28} (prepared in Example 28), 0.118 g (1.5 mmol) of pyridine, 0.069 g (1 mmol) of hydroxylamine hydrochloride ($NH_2OH.HCl$), 2 ml of methanol and 4 ml of water is allowed to react at room temperature for 1.5 hours under stirring. The precipitated crystals are collected by filtration to give 0.170 g of the product I_{29}, yield 90.9%, mp. 185–186°C. This is recrystallized from acetone to give 0.130 g of grayish white crystals, yield 69.5%, mp. 188–189°C.

Anal. Calcd. (%) for $C_{14}H_{13}Cl_2NO_3S_2$
: C 44.45 H 3.46, Cl 18.75, N 3.70, S 16.95,
Found (%) : C 44.25, H 3.60, Cl 18.60, N 3.60, S 16.84.
IR νmax (Nujol) : 3360, 1615, 1606 cm $^{-1}$.
NMR δppm (DMSO d_6) : 2.50 (s), 2.60 (s) (shaded by DMSO signal, 3.10–3.73 (2H, m), 5.37–5.77 (1H, m), 6.42 (1H, s), 7.40 (1H), 7.57 (1H, d), 11.35 (1H, s).

Example 30

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxynitrile



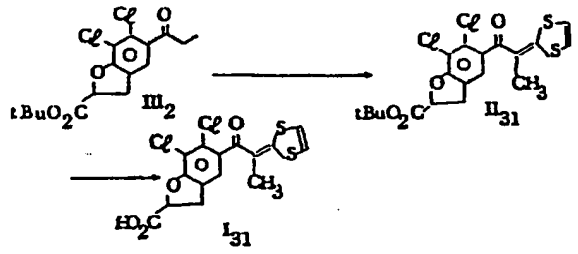
I_{29} I_{30}

To a solution of 0.34 g (0.9 mmol) of the compound I_{29} (prepared in Example 29) and 0.08 g (1.0 mmol) of pyridine in a mixture of 5 ml of ether and 5 ml of tetrahydrofuran is added 0.158 g (0.9 mmol) of phenylchlorosulfate (Ph-O-SOCl) [ω: E. Bissingene JACS *70* 2664 (1948)] at 0°C under stirring. The mixture is allowed to react in accordance with the method as disclosed in J. G. Krause et. al. Synthesis 502 (1975). The reaction mixture is purified by liquid chromatography on a Lober column (Type B) chloroform/benzene/ethyl acetate (3/1/1) to give 0.130 g of the compound I_{30}, yield 40.2%, mp. 205–209°C. This is recrystallized from acetone to give 0.100 g of grayish white crystals, yield 31.0%, mp. 209–210°C.

Anal. Calcd. (%) for $C_{14}H_{11}Cl_2NO_2S_2$
: C 46.67 H 3.08, Cl 19.68, N 3.89, S 17.80,
Found (%) : C 46.61, H 3.15, Cl 19.62, N 4.02, S 17.96.
IR νmax (Nujol) : 1622, 1605 cm $^{-1}$.
NMR δppm (DMSO d_6) : 2.50(s), 2.58 (s) (shaded by DMSO signal), 3.57–3.90 (2H, m), 6.05 (1H, s), 6.42 (1H, m), 7.48 (1H).

Example 31

6,7-Dichloro-5-[2-(1,3-dithiol-2-ylidene)propynoyl]-1-benzofuran-2-carboxylic acid.



III_2 II_{31} I_{31}

To a suspension of 0.255 g (6.2 mmol) of 65.6% sodium hydride in 5 ml of dry acetonitrile is added a solution of 1.50 g (4.3 mmol) of the compound III_2 in 5 ml of acetonitrile under nitoregen flow while being stirred at room temperature. Subsequently, 1 ml of N,N-dimethylacetoamide is added to the mixture and the resulting mixture is allowed to react for 1.5 hours and then 1.44 g (5.2 mmol) of 2-methylthio-1,3-dithioliodide [L. Russell Melky et. al. JOC *39*, 2456 (1974)] is added to the reaction mixture and this mixture is allowed to react for 6 hours. The reaction product is purified by liquid chromatography on a Lober column (Type B) with a mixture of n-hexane/ethyl acetate (7/3) to give 0.4 g of a crude product, yield 20.6%. This is treated with ether to give 0.284 g of the compound II_{31}, yield 14.7%, 175–177°C.

NMR δppm ($CDCl_3$): 1.50(9H, s), 3.07–3.73 (2H, m), 5.08–5.37 (1H, m), 6.87–7.13 (3H, m).

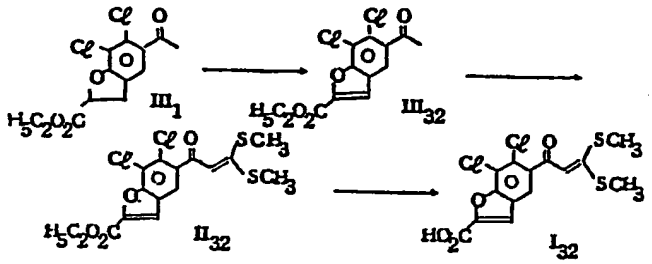
To 0.41 g (0.9 mmol) of the compound II_{31} is added 4.1 ml of trifluoroacetic acid and the mixture is allowed to react at room temperature for an hour under stirring.

The solvent is evaporated and the residue is treated with n-hexane to give 0.36 g of the compound I_{31}, yield 100%, mp. 266–270°C (dec.).

Anal. Calcd. (%) for $C_{13}H_{10}Cl_2O_4S_2$
: C 46.28 H 2.59, Cl 18.22, S 16.47,
Found (%) : C 46.19, H 2.78, Cl 18.24, S 16.35.
IR : νmax (Nujol) 2650, 2560, 1712 (sh 1750), 1608, 1583.

Example 32

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-1-benzofuran-2-carboxylic acid.



A mixture of 1.50 g (5.0 mmol) of ethyl 5-aceyl-6,7-dichloro-2,3-dihydro-1-benzofuran-2-carboxylate III_1 (William. Hoffman. et. al., J. Med. Chem. *24* 865 (1981)), 0.025 g (0.1 mmol) of benzoperoxide, 0.9 g (5.1 mmol) of N-bromosuccinimide and 50 ml of carbon tetrachloride is allowed to react according to the method disclosed in the above-mentioned literature.

The reaction product is treated in 0.6 ml (5.2 ml) of 1,5-diazabicyclo[4.3.0]none-5-ene and 12.5 ml of dimethyl sulfoxide, mentioned in the same literature, to give 1.20 g of the compound III_{32}, yield 80.5%, mp. 120–122°C.

NMR δppm ($CDCl_3$): 1.45(3H, t), 2.67 (3H, s), 4.47(2H, q), 7.53 (1H, s), 7.73 (1H, s).

From 1.20 g (4.0 mmol) of the compound III_{32} is prepared 0.66 g of the compound II_{32}, with treating in the same manner mentioned in Example 1, yield 40.9%, mp. 184–185°C.

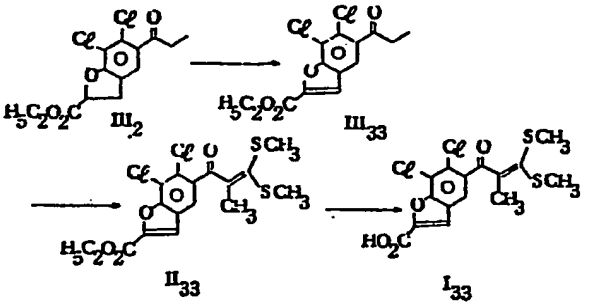
NMR δppm ($CDCl_3$): 1.42(3H, t), 2.50 (3H, s), 2.57 (3H, s), 4.45 (2H, q), 6.40 (1H, s), 7.50 (1H, s), 7.68 (1H, s).

According to Example 1, 0.30 g of (0.7 mmol) of the compound II_{32} is hydrolyzed with alkali to give 0.279 g of the product I_{32}, mp. 266–271°C (dec.). This is recrystallized from acetone to give 0.258 g of grayish white crystals, yield 92.4 %, mp. 268–271°C.

Anal. Calcd. (%) for $C_{14}H_{10}Cl_2S_4$
: C 44.57, H 2.67, Cl 18.80, S 17.00,
Found (%) : C 44.40, H 2.83, Cl 18.83, S 16.70.
IR νmax (Nujol) : 2700, 2600, 2520, 1700, 1627, 1608 cm^{-1}.

Example 33

6,7-Dichloro-5-[2-methyl-3,3-bis(methylthio)propenoyl]-1-benzofuran-2-carboxylic acid



In the same manner as in Example 32 is treated 3.0 g (9.5 mmol) of the compound III_2 to give 2.24 g of the compound III_{33}, yield 75.6%, mp. 107–108°C.

NMR δppm ($CDCl_3$): 1.23 (3H, t), 1.43 (3H, t), 2.90 (2H, q), 4.45 (2H, q), 7.53 (1H, s), 7.63 (1H, s).

In the same manner as in Example 1 is treated 1.70 g (5.4 mmol) of the compound III_{33} to give 0.50 g of the compound II_{33}, yield 22.1%

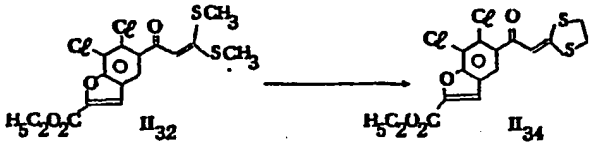
NMR δppm ($CDCl_3$): 1.43 (3H, t), 1.88 (3H, s), 2.30 (3H, s), 2.37 (3H, s), 4.45 (2H, q), 7.52 (1H, s), 7.72 (1H, s).

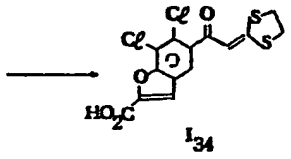
In the same manner as in Example 1 is hydrolyzed 0.095 g (0.2 mmol) of the compound II_{33}

to give 0.084 g of the compound I_{33}, yield 95.5%, mp. 216–218°C (dec.).
This is recrystallized from ethyl acetate to give 0.074 g of grayish white crystals, yield 84.1%, mp. 218–219°C.

Anal. Calcd. (%) for $C_{15}H_{12}Cl_2O_4S_2$
: C 46.04 H 3.09, Cl 18.12, S 16.39,
Found (%) : C 45.98, H 3.28, Cl 18.19, S 16.18.
IR : νmax (Nujol) 2710, 2600, 2500, 1714, 1692, 1625, 1604.

Example 34
6,7-Dichloro-5-[2-(1,3-dithiolan-2-yliden)acetyl]-1-benzofuran-2-carboxylic acid





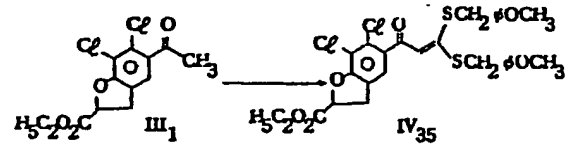
In the same manner as in Example 19 is treated 0.350 g (0.9 mmol) of the compound II_{32} (prepared in Example 32) to give 0.120 g of the compound II_{34}, yield 34.5% mp, 235–237°C.

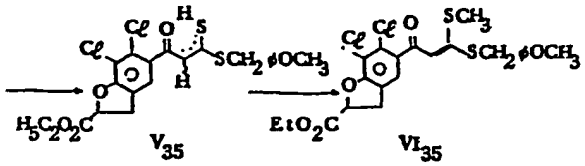
NMR δppm ($CDCl_3$): 1.45(3H, t), 3.52 (4H, br), 4.50 (2H, q), 6.93 (1H, s), 7.58 (1H, s), 7.72 (1H, s).

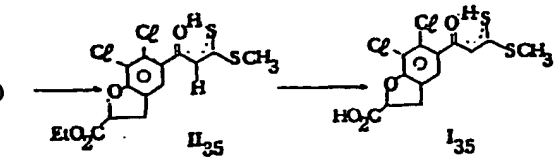
In the same manner as mentioned in Example 32 is hydrolyzed 0.120 g (0.3 mmol) of the compound II_{34} to give 0.112 g of the compound I_{34}, yield 100% mp. 300–305°C (dec.). This is recrystallized from methyl ethyl ketone to give 0.105 g of grayish white crystals, yield 93.8%, mp. 305–309°C (dec.).

Anal. Calcd. (%) for $C_{14}H_8Cl_2O_4S_2$
: C 44.81 H 2.15, Cl 18.90, S 17.09,
Found (%) : C 44.91, H 2.40, Cl 18.91, S 16.89.
IR νmax (Nujol) : 2570, 1714, 1611, 1580 cm^{-1}.

Example 35
6,7-Dichloro-5-[2-methyl-3-mercapto-3-(methylthio)propanoyl-2,3-dihydro-1-benzofuran-2-carboxylic acid







The compound III, (7.0 g, 23.1 mmol) is allowed to react with 2.10 g (56.9 mmol) of 65% sodium hydride, 14 g (69.6 mmol) of 4-methoxyl-benzylbromide, 5.3 (69.6 mmol) of carbon

disulfide, 90 ml of dry ether, 4.7 ml of N,N-dimethylacetoamide and a catalytic amount of potassium iodide in the same manner as mentioned in Example 1 to give 8.1 g of the compound IV_{35}, yield 56.6%.

NMR δppm ($CDCl_3$): 1.28(3H, t×2), 3.08–3.83 (8H, m), 4.03–4.43 (6H, m), 5.12–5.40 (1H, m), 6.50 (1H, s), 6.63–7.37 (1H).

To 5.50 g (8.9 mmol) of the compound IV_{35} are added 11 ml of anisole and 11 ml of trifluoroacetic acid, and the mixture is allowed to reacted under stirring at room temperature for 2 hours. The solvent is evaporated and the resulting residue is chromatographed on a 40 g silical-gel column with a mixture of n-hexane/benzene (7/3), with n-hexane/benzene (7/3) (F-1, 400 ml), n-hexane/benzene (1/1) (F-2, 200 ml), n-hexane/benzene (2/3) (F-3, 200 ml) and benzene (F-4, 500 ml) as eluates in order. From the last fraction, 3.93 g of the compound V_{35} is recovered, yield 88.8%.

NMR δppm ($CDCl_3$): 1.30(3H, t), 3.17–3.70 (2H, m), 4.08–4.43 (4H, m), 5.18–5.47 (1H, m), 6.57 (1H, s), 6.70–7.43 (5H), 14.94 (1H, s).

To a suspension of 1.9 g (3.8 mmol) of the compound V_{35} and 0.79 g (5.7 mmol) of powdery potassium carbonate in 10 ml of N,N-dimethylformamide, under nitrogen flow while being stirred at room temperature is added 1.08 g (7.6 mmol) of methyl iodide, the mixture is allowed to react for 2 hours. Insoluble material is filtered off and benzene is added to the filtrate. The benzene solution is washed with water (4 times), dried over anhydrous magnesium sulfate and evaporated to give a residue which is treated by high performance liquid chromatography on a Lober column (Type B) with a benzene/ethyl acetate (10/1) mixture to give 1.80 g of the compound VI_{35}, yield 92.0%,

NMR δppm ($CDCl_3$): 1.30(3H, t), 2.50 (3H, s), 3.10–3.70 (2H, m), 3.78 (3H, s), 4.07–4.47 (4H, m), 5.17–5.45 (1H, m), 6.43, 6.57 (1H, s×2), 6.73–7.40 (5H).

To 1.81 g (3.5 mmol) of the compound VI_{35} are added 3.6 ml of anisole and 3.6 ml of trifluoroacetic acid, and the mixture is allowed to react at room temperature for 2 hours under stirring. Toluene is added to the reaction mixture and then the resulting mixture is evaporated to give a residue. The residue is chromatographed on a column of 18 g of silica-gel with n-hexane/benzene (7/3) mixture, with n-hexane/benzene (7/3) (F-1, 600ml), n-hexane/benzene (1/1) (F-2, 200ml), and n-hexane/benzene (2/3) (F-3, 400ml) as eluents in order. From the last fraction i.e. F-3, 1.30 g of the compound II_{35} is recovered, yield 93.8%.

IR νmax ($CHCl_3$): 1755, 1730, 1608, 1585 cm^{-1}.
NMR δppm ($CDCl_3$): 1.30(3H, t), 2.62 (3H, s), 3.12–3.95 (2H, m), 4.25 (2H, q), 5.22–5.65 (1H, m), 6.60 (1H, s), 7.28 (1H), 14.95 (1H,s).

To 0.24 g (0.6 mmol) of the compound II_{35} are added 3 ml of ethanol and 1.2 ml of 1N potassium hydroxide, the mixture is allowed to react at room temperature for an hour. The solution is evaporated to give a residue to which is added 10% hydrochloric acid to adjust to pH 3. The precipitated crystalline solid is collected by filtration, washed with water, and dried to give 0.213 g of the compound I_{35}, yield 95.5%, mp. 182–185°C (dec.). This is recrystallized from ethanol to give 0.113 g of yellow crystals, yield 5o.5%, mp. 185–186°C (dec.).

IR νmax (Nujol): 3040, 2750, 2660, 2540, 1723 (sh 1708), 1608, 1584 cm^{-1}
Anal. Calcd. (%) for $C_{13}H_{10}Cl_2O_4S_2$
: C 42.75 H 2.76, Cl 19.41, S 17.56,
Found (%) : C 42.84, H 2.88, Cl 19.37, S 17.40.

Examples 36 and 37

The compounds I_{35}, I_{37} and their intermediates are prepared in the same manner as in Example 35, whose physical constants and reaction conditions are shown in the following Table 3 (Nos. 1 to 5).

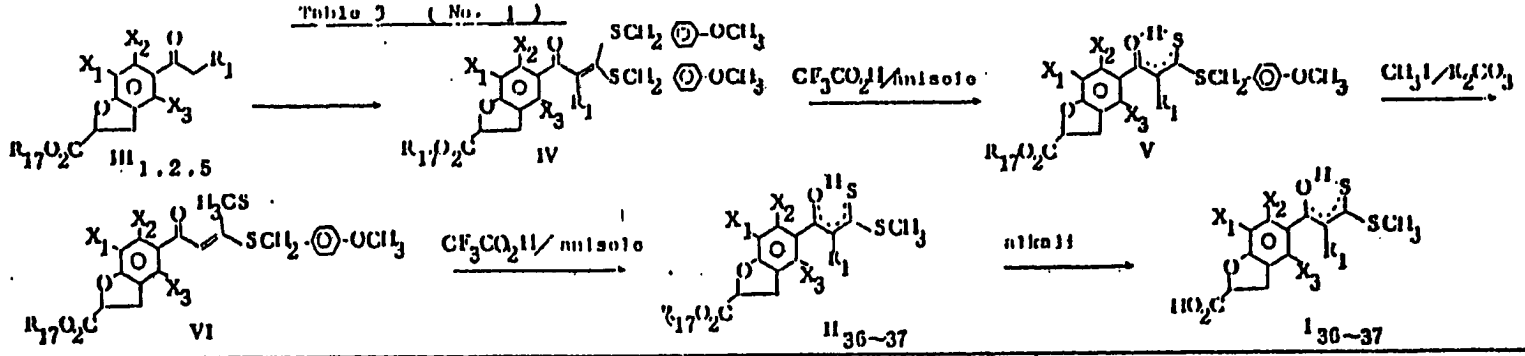


Table 3 (No. 1)

Example Nos.	(III) R_1	(III) R_{17}	(III) X_1	(III) X_2	(III) X_3	Amount Used g (mmol) (III)	NaH	CS_2	R_5Br or Cl-◎-CH_2Br	Solvent and other DME	DMA	Temp	Time	Yield (%)	NMR δ ppm $CDCl_3$ (IV)
36	CH_3	C_2H_5	Cℓ	Cℓ	H	4.0 (12.6)	1.11 (30.3)	2.87 (37.7)	7.50 (37.3)	4.0	2.59	25 ~ 27°	9.6	9.4 ※v (9.9%)	1.32(3H,t)2.07(S,3H)3.27~3.60(2H,m)3.77(3H,S) 4.00(2H,S)4.25(2H,q)5.17~5.45(1H,m) 6.67~7.37(9H,m)
37	H	CH_3	Cℓ	Cℓ	H	3.40 (13.8)	1.04 (28.2)	3.30 (43.3)	6.0 (39.8)	3.3	2.35	〃	〃	32.5	3.20~3.93(11H,m)4.12(2H,S)4.20(2H,S) 5.13~5.50(3H,m)6.53(1H,S)6.67~7.37(9H)

Table 3 (No. 2)

Example Nos.	Amount Used g (mmol) (IV)	CF_3CO_2H	anisole	Temp	Time	Yield (%)	NMR δ ppm $CDCl_3$ (V)
36	0.55 (0.9)	1.1 ml	1.1 ml	25°	2	99.5	1.30(t,3H)1.62(d)1.93(S)3H 6.67~7.43(9H,m) 3.17~3.70(2H,m)3.78(3H,S) 4.07~4.17(4H,m)4.90~5.53(1H,m)
37	2.71 (4.5)	5.4	5.4	〃	2	85.7	3.20~3.90(8H,m)4.43(2H,S)5.20~5.65(1H,m) 6.53(S,1H)6.72~7.37(5H,m)14.93(1H,S)

Table 3 (No. 3)

Example Nos.	Amount Used (V)	g (mmol) K_2CO_3	CH_3I	Solvent	Temp.	Time	Yield (%)	NMR $\delta^{CDCl_3}_{ppm}$ (VI)
36	0.2 (0.6)	0.162 (1.2)	0.247 (1.7)	DMF 3 ml	25°	6	64.9	
37	1.86 (9.8)	1.06 (7.7)	1.09 (7.7)	MeCN 6	25°	1	94.2	2.47 (3H, S) 3.07~3.83 (8H, m) 4.10 (1H, S) 4.22 (1H, S) 5.17~5.45 (1H, m) 6.40 (S) 6.53 (S) (1H) 6.70~7.40 (5H, m)

Table 3 (No. 4)

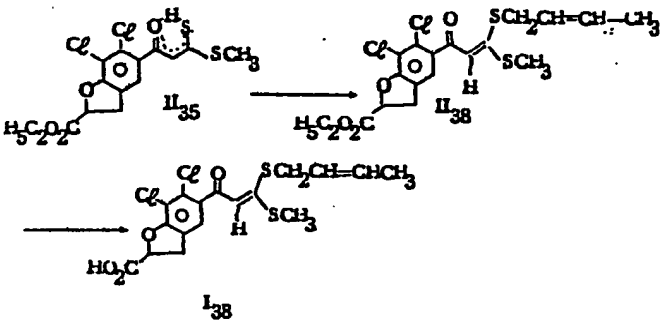
Example Nos.	Amount Used (VI)	g (mmol) CF_3CO_2H	anisole	Temp.	Time	Yield (%)	NMR $\delta^{CDCl_3}_{ppm}$ (II)
36	0.38 (0.3)	0.3 ml 6	0.3 ml 6	25°	2	71.9	1.32 (t, 3H) [1.62 (d) 1.98 (S), 3H] [2.58 (S) 2.65 (S), 3H] 3.13~3.90 (2H, m) 4.26 (2H, q) 5.05~5.53 (1H, m) 6.83 (1H) 7.02~7.23 (1H, m)
37	1.75 (3.5)	3.5	3.5	25	2	90.2	2.05 (3H, S) 3.13~3.77 (2H, m) 3.82 (3H, S) 5.23~5.52 (1H, m) 6.62 (1H, S) 7.30 (1H) 14.95 (1H, S)

Table 3 (No. 5)

Example Nos.	Amount Used (II)	g (mmol) KOH	Solvent	Temp.	Time	Yield (%)	Re-crystal from	mp (dec)	Calcd. / Found C	H	Cl	S	IR: ν^{Nujol}_{max}
36	0.1 (0.2)	0.041 (0.7)	ethanol water	25	1	53.8	ethanol	175~177°	44.33 / 44.25	3.19 / 3.24	18.70 / 18.59	16.91 / 16.63	3100 (br), 2640, 2540, 1710, 1610, 1565

Example 38

6,7-Dichloro-5-[3-(chlorothio)-3-(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-3-carboxylic acid



To 0.56 g (1.4 mmol) of ethyl 6,7-chloro-5-[3-(mercapto)-3-(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxylate (prepared in Example 35) are added 0.387 g (2.8 mmol) of dry potassium carbonate, 0.250 g (1.9 mmol) of crotyl bromide and 5 ml of N,N-dimethylformamide, and the mixture is allowed to react at room temperature for an hour while being stirred. Insoluble material is filtered off and benzene is added to the filtrate. The filtrate is washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue is purified by high performance liquid chromatography on a Lober column (Type B) with a benzene/ethyl acetate (10/1) mixture to give 0.578 g of the oily compound II_{38}, yield 90.7%.

NMR δppm ($CDCl_3$): 1.32(3H, t), 1.72 (3H, d), 2.50 (3H, s), 3.10–3.90 (4H, m), 4.43 (2H, q), 5.20–6.03 (3H, m), 6.55 (1H, s), 7.27 (1H).

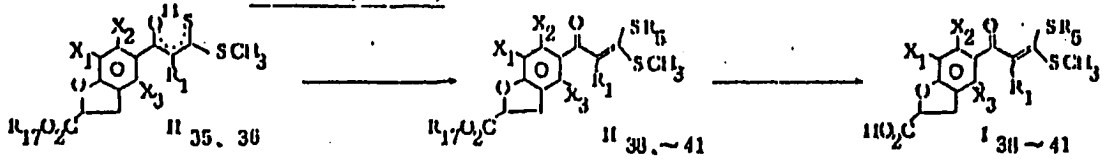
To 0.185 g (0.4 mmol) of the compound II_{38} are added 0.82 ml (0.8 mmol of 1N potassium hydroxide and 2 ml of ethanol. The mixture is allowed to react at room temperature for an hour. The solvent is evaporated to give a residue, to which ether is added. The mixture is adjusted to pH 3 with 10% hydrochloric acid while being stirred under ice-cooling. The ether layer is separated, washed with water, dried over dry magnesium sulfate and then evaporated to give 0.14 g of the objective product I_{38}, yield 80.9%, mp. 166–169°C. This is recrystallized from ethyl acetate to give 0.10 g of grayish white crystals I_{38}, yield 57.8 %, mp. 175–176°C.

Anal. Calcd. (%) for $C_{17}H_{16}Cl_2O_4S_2$
: C 48.69 H 3.85, Cl 16.91, S 15.29,
Found (%) : C 48.52, H 3.85, Cl 16.98, S 15.12.
IR νmax (Nujol) : 2700, 2580, 2480, 1746, 1608 cm^{-1}.

Examples 39–41

The compounds are prepared in the same manner as in Example 38, whose physical constants and reaction conditions are shown in Table 4 (Nos. 1 and 2).

Table 4 (No. 1)



II 35, 36 → II 38~41 → I 38~41

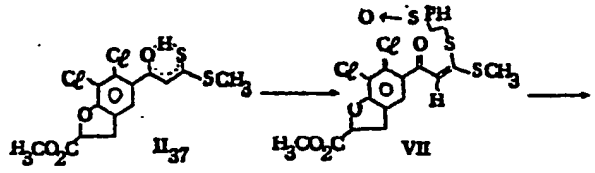
Example Nos.	R_{17}	R_1	X_1	X_2	X_3	Amount Used g (mmol) II 35,36	R_5Br	K_2CO_3	Solvent DMF	Temp.	Time	% Yield	Recrystal from	m.p.	NMR
39	C_2H_5	CH_3	Cℓ	Cℓ	H	0.33 (0.8)	C_2H_5Br 0.100 (1.0)	0.168 (1.2)	DMF 7 ml	25	5	58.6	—	—	(0.95(t)1.25(t)3H)1.92(3H,t)2.27(3H,S) (2.36(S)2.02(S)3H)2.58(q)2.83(q)2H) 3.17~3.95(2H,m)4.30(q,2H)5.23~5.57(1H,m) 7.50~7.33(1H)
40	〃	H	〃	〃	〃	0.16 (0.4)	$BrCH_2{\equiv}CH$ 0.07 (0.6)	1.10 (0.8)	2 ml	25	1	88.0	—	—	1.30(3H,t)2.28~2.47(1H,m)2.52(3H,S)3.15~ 3.95(2H,m)4.25(2H,q)5.16~5.45(1H,m) (6.33(S)6.62(S)1H)7.22(1H)
41	CH_3	H	〃	〃	〃	0.267 (0.7)	$ClCH_2CONH_2$ 0.098 (1.0)	0.198 (1.4)	4 ml	25	5	33.8		174 ~ 175°	2.53(singlet 3H,S) 3.20~3.47(2H,m)3.73 3.78 (3H,S-S)5.45~5.73(1H,m)6.43(1H,S) 7.17(1H,br)7.40(1H)7.58(1H,br)

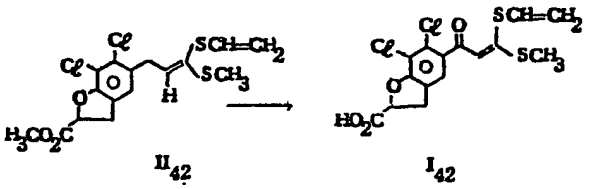
Table 4 (No. 2)

Example Nos.	Amount Used (II)	KOH	Solvent H_2O	ethanol	Temp.	Time	Recrystal from	m.p.	% Yield	Molecular formula	C	H	Cℓ	S	N	IR
39	0.33 (0.8)	0.085 (1.5)	3.6		25	1	ether/ hexane	125 ~ 126°	50.3	$C_{16}H_{16}Cl_2O_4S_2$	47.18 47.04	3.96 4.02	17.41 17.46	15.74 15.57	— —	3020, 1763, 1630, 1600
40	0.145 (0.3)	0.020 (0.5)	2.5		25	1	ethyl acetate	135 ~136° (dec.)	20.4	$C_{16}H_{12}Cl_2O_4S_2$	47.65 47.80	3.00 3.12	17.58 17.78	15.90 16.05	— —	3285, 1730, 1700, 1627, 1603
41										$C_{16}H_{15}Cl_2NO_6S_2$	44.04 43.72	3.47 3.56	16.25 16.27	14.70 14.66	3.21 3.11	3430,3365,3290,3185, 1755,1682,1625,1603

Example 42

6,7-Dichloro-5-[3-(methylthio)-3-(vinylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid





To 0.30 g (0.8 mmol) of the compound II_{37} (prepared in Example 37) are added 0.221 g (1.6 mmol) of powdery potassium carbonate and 3 ml of acetonitrile while being stirred at room temperature, and 0.276 g (1.2 mmol) of 2-bromoethyl phenyl sulfide is added thereto. The mixture is allowed to react for 16 hours and then treated in the same manner as in Example 38 to give 0.4 g of the compound VII, yield 95.2%.

NMR δppm ($CDCl_3$): 2.47(3H, s), 3.13–3.68 (6H, m), 3.80 (3H, s), 5.17–5.55 (1H, m), 6.32, 6.43 (1H, s-s), 7.18–7.72 (6H, m).

To 0.4 g (0.8mmol) of the compound VII is added 8 ml of toluene and the mixture is allowed to react on an oil bath (135–140°C) for 16 hours while being stirred. The reaction product is treated by high performance liquid chromatography on a Lober column (Type A) with dichloromethane to give 0.213 g of the compound II_{42}, yield 69.8%. mp. 101–102°C.

NMR δppm ($CDCl_3$): 2.47, 2.52 (3H, s-s), 5.20–5.93 (3H, m), 6.33–7.13 (2H, m), 7.30 (1H).

The above product is hydrolyzed with an alkali in the same manner as in Example 1 without purification to give 0.170 g of the compound I_{42}, yield 88.1%, mp. 160–168°C, which is recrystallized from ethyl acetate to give 0.133 g of grayish white crystals, yield 68.9%, mp. 170–172°C.

Anal. Calcd. (%) for $C_{15}H_{12}Cl_2O_2S_2$: C 46.04 H 3.09, Cl 18.12, S 16.39,

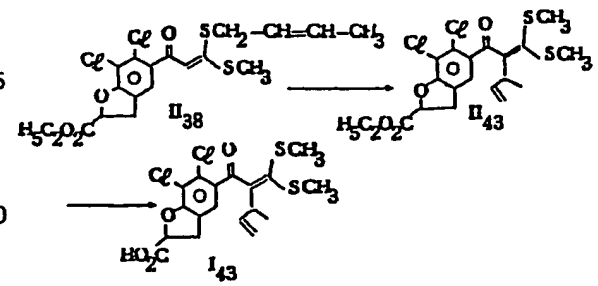
Found (%) : C 45.83, H 3.13, Cl 18.05, S 16.29.

IR νmax (Nujol) : 2940, 2560, 1704, (3h, 745), 1632, 1605cm $^{-1}$.

NMR δppm (ME_2CO d=6) : 2.58(3H, s), 3.23–4.10(2H,m), 5.30–6.30(4H,m), 6.57–7.23(2H,m), 7.35(1H).

Example 43

6,7-Dichloro-5-[2-(1-methylallyl)-3,3-bis(methylthio)propenoyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid



Under a reduced pressure (4/100–8/100 mmHg), 0.32 g (0.7 mmol) of the compound II_{38} is heated on an oil bath (200°C) for 5 minutes. The reaction product is chromatographed on a

Lober column (Type A) with dichloromethane to give 0.173 g [containing 0.056 g (17.5%) of II_{38} remaining unchanged] of an oily material, to which 0.10 g (0.7 mmol) of powdery potassium carbonate, 0.085 g (1.4 mmol) of iodomethane and 2 ml of N,N-dimehtylacetoamide are added. The resulting mixture is allowed to react at room temperature for 14 hours while being stirred. The reaction product is chromatographed on a Lober column (Type A) with dichloromethane as an eluent to give 0.115 g of the compound II_{43} as an oil, yield 43.7%.

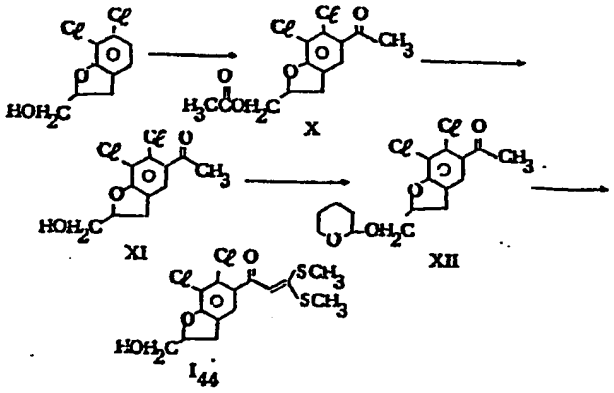
NMR δppm ($CDCl_3$): 1.18–1.43 (6H, m), 2.00 (3H, s), 2.35 (3H, s), 3.15–3.72 (3H, m), 4.27 (2H, q), 4.87–6.23 (4H, m), 7.38 (1H).

To 0.115 g (0.2 mmol) of the compound II_{43} are added 0.5 ml of 1N potassium hydroxide and 1 ml of ethanol, and the mixture is hydrolyzed to give 0.10 g of the objective product I_{43}, yield 91.7%, mp. 155–159°C. This is recrystallized from a mixture of isopropyl ether/n-hexane to give 0.056 g of grayish white crystals, yield 51.4%, mp. 162–164°C.

Anal. Calcd. (%) for $C_{18}H_{18}Cl_2O_4S_2\frac{1}{4}H_2O$
: C 49.37 H 4.26, Cl 16.20, S 14.65, H_2O 1.03
Found (%) : C 49.49, H 4.18, Cl 16.47, S 14.48, H_2O 0.80
IR νmax (Nujol) : 3260 (br), 1760, 1605, 1598 cm $^{-1}$.

Example 44

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-yl methanol



To a solution of 4.0 g (18.3 mmol) of 6,7-dichloro-2,3-dihydro-1-benzofuran-2-yl methanol (W. F. Hoffmann et. al. J. Med. Chem. *24*, 865–873 (1981)) and 3.70 g (47.1 mmol) of acetyl chloride in 40 ml of dichloromethane is added in small portions 7.3 g of dry aluminium chloride over a 0.5 hour duration while being stirred under ice-cooling, and the mixture is allowed to react at room temperature for an hour. The reaction product is chromatographed on a Lober column (Type B) to give 4.98 g of the compound X_{44}, yield 89.9% mp. 90–93°C. This is recrystallized from ethyl acetate to give 4.98 g of grayish white crystals, yield 89.9%, mp. 93–94°C.

Anal. Calcd. (%) for $C_{13}H_{12}Cl_2O_4$
: C 51.50 H 3.99, Cl 23.29,
Found (%) : C 51.36, H 3.98, Cl 23.26.
IR : νmax (Nujol) 1735, 1685 cm $^{-1}$.
NMR δppm ($CDCl_3$) : 2.07 (s,3H), 2.60 (3H,s), 2.83–3.70 (2H, m), 4.32 (2H, d), 4.97–5.45 (1H,m), 7.32 (1H).

To 4.78 g (15.8 mmol) of the compound X_{44} are added 20ml of methanol and 20 ml of 1N potassium hydroxide, and the mixture is allowed to react for an hour. The solvent is removed by evaporation and the residue is dissolved in dichloromethane. The dichloromethane layer is washed with water (2 times), dried over anhydrous magnesium sulfate, and decolored by chromatography on 4 g of silical-gel to give 3.51 g of the compound X I_{44}, yield 85.2 %, mp. 102–105°C. This is recrystallized to give grayish white crystals, mp. 105–106°C.

Anal. Calcd. (%) for $C_{11}H_{10}Cl_2O_3$
: C 50.60 H 3.86, Cl 27.16,
Found (%) : C 50.39, H 3,80, Cl 26.96.
IR : νmax (Nujol) 3500(br), 1677 cm^{-1}.
NMR : 2.58 (3H,s); 2.83–3.63 (3H, m+D_2O 2H), 3.70–4.18 (2H, m), 4.85–5.33(1H,m), 7.28(1H).

To a solution of 3.30 g (12.6 mmol) of the compound X I and 2.13 g (25.3 mmol) of dihydropyrane in 35 ml of chloroform is added a catalytic amount of p-toluenesulfonic acid, and the mixture is allowed to react at room temperature for 3 hours while being stirred. Chloroform is evaporated and the residue is dissoved in ether, poured into an amnonia (2 ml)-ice mixture. The ether layer is separated, dried over anhydrous magnesium sulfate and evaporated to give 4.39 g of the compound X II, yield 100%.

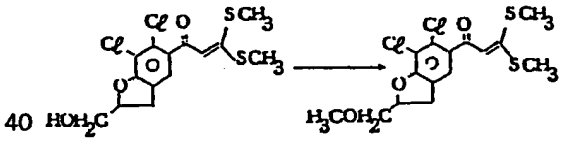
NMR: δppm 1.58 (6H,br), 2.60(3H,s), 2.93–4.13 (6H,m), 4.62(1H,br), 4.95–5.43(1H,m), 7.35(1H).

In the same manner as in Example 1 is treated 2.30 g (6.7 mmol) of the compound X II. To the reaction mixture are added 5 ml of anisole and 5 ml of trifluoroacetic acid and the mixture is allowed to react at room temperature while bing stirred. The reaction product is treated by chromatography on a Lober column, crystallized from n-hexane, and recrystallized from ethyl acetate to give 0.47 g of pale yellow crystalline solid, yield 19.3%, mp. 120–121°C.

Anal. Calcd. (%) for $C_{14}H_{14}Cl_2O_3S_2$
: C 46.03 H 3.86, Cl 19.41, S 17.56
Found (%) : C 45.84, H 4.03, Cl 19.46. S 17.52
NMR δppm ($CDCl_3$) : 2.03 (1H,br), 2.50(3H,s), 2.53(3H,s), 3.12–340(2H,m), 3.95(2H,br-t,D_2Ot), 4.85–5.32(1H,m), 6.48(1H,s), 7.27(1H).

Example 45

3,3-Bis(methylthio)-1-[6,7-dichloro-2-methoxymethyl-2,3-dihydro-1-benzofruan-5-yl]-acrylaldehyde



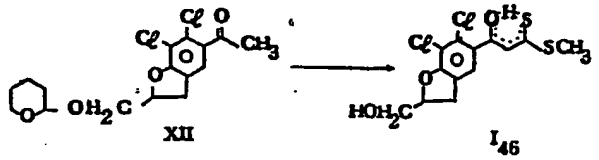
I_{44} I_{45}

To a suspension of 0.037 g of 65% sodium hydride in DMF is added a solution of 0.36 g (1 mmol) of the compound I_{44} in 2 ml DMF under nitrogen atmosphere at room temperature while being stirred. Subsequently, an excess amount of methyl iodide added thereto and the mixture is allowed to react for 2 hours. The reaction product is chromatographed on a Lober column to give 0.065 g of the compound I_{45}, yield 17.4%, mp. 132–134°C, which is recrystallized from isopropyl ether-hexane to give 0.05 g of pale yellow crystalline product, yield 13.5%, 135–136°C.

Anal. Calcd. (%) for $C_{15}H_{16}Cl_2O_3S_2$
: C 47.49 H 4.56, Cl 18.69, S 16.91
Found (%) : C 47.38, H 4.30, Cl 18.85, S 16.86.
NMR δppm ($CDCl_3$) : [2.48(s), 2.53(s), 6H], 3.10–3.50 (5H,m), 3.63(2H,d), 4.87–5.37(1H,m), 6.47(1H,s), 7.25(1H).

Example 46

6,7-Dichloro-5-[3-mercapto-3-(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-yl-methanol



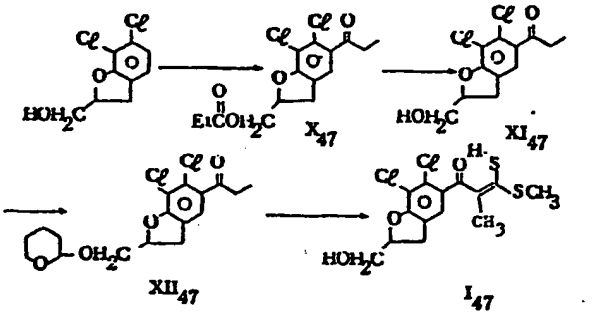
XII I_{46}

Using 3.43 g (9.9 mmol) of the compound X II, 2.27 g (29.8 mmol) of carbon disulfide, 6.0 g (29.8 mmol) of 4-methoxybenzylbromide, 0.88 g (23.8 mmol) of 65% sodium hydride, 1.98 ml of N,N-dimethylacetoamide and 10 ml of ether, the reaction is made in the same manner as in Example 35. A portion (1.6 g) of 2.7 g of the reaction product [the remains (1.1 g) are used in Example 49] is allowed to react with 3.2 ml of anisole and 4 ml of trifluoroacetic acid for 1.5 hours and then to react with methyl iodide in the presence of anhydrous potassium carbonate in acetonitrile for 0.5 hours. The product is treated with a trifluoroacetic acid/anisole mixture and purified by using a Lober column to give 0.24 g (yield 11.7%) of the compound I_{46}, m.p. 100–102°C. This is recrystallized from isopropyl ether to give 0.20 g (yield 9.7%) of pale yellow crystals, m.p. 101–102°C.

Anal. Calcd. (%) for $C_{13}H_{12}Cl_2O_3S_2$: C 44.45 H 3.44, Cl 20.19, S 18.25
Found (%) : C 44.21, H 3.48, Cl 20.37, S 18.18.
IR νmax (Nujol) : 3400 (br), 1595, 1609 cm^{-1}.
NMR δppm ($CDCl_3$) : 2.02 (br, 1H, disappeared by addition of D_2O, 2.63 (3H, s), 2.92–3.43(2H, m), 3.67–4.10 (2H, m), 4.82–5.38 (1H, m), 6.62 (1H, s), 7.48 (1H), 14.97 (1H, s).

Example 47

6,7-Dichloro-5-[2-methyl-3-mercapto-3-(methylthio)propenoyl]-2,3-dihydro-1-benzofuran-2-yl-methanol



X_{47} XI_{47} XII_{47} I_{47}

6,7-Dichloro-2,3-dihydro-1-benzofuran-2-yl-methanol (6.0 g, 27.4 mmol) is allowed to react with 7.6 g (82.1 mmol) of propyonyl chloride (82.1 mmol), 11.0 g (82.5 mmol) of anhydrous aluminium chloride, and 30 ml of dichloromethane in the same manner as in Example 44 to give 7.10 g (yield 82.7%) of the compound X_{47}, m.p. 49–50°C.

Anal. Calcd. (%) for $C_{15}H_{16}Cl_2O_4$: C 54.39 H 4.87, Cl 21.41,
Found (%) : C 54.19, H 4.92, Cl 21.37.
IR νmax (Nujol) : 1742, 1697, 1607 cm^{-1}.
NMR δppm ($CDCl_3$) : 1.10 (t, 3H), 1.17 (t, 3H), 2.35(2H, q), 2.92 (2H, q), 3.10–3.70 (2H, m), 4.30 (2H, d), 4.93–5.43 (1H, m), 7.17 (1H).

The compound X_{47} (7.1 g, 21.4 mmol) is treated with 14 ml of ethanol and 26 ml of 1N-potassium carbonate in the same manner as in Example 44 to give 5.40 g (yield 91.5%) of the compound X I_{47}, m.p. 94–95°C.

Anal. Calcd. (%) for $C_{12}H_{12}Cl_2O_3$
: C 52.38 H 4.40, Cl 25.77,
Found (%) : C 52.15, H 4.45, Cl 25.63.
IR νmax (Nujol) : 3510, 3430, 1682, 1654, 1604 cm $^{-1}$.
NMR δppm ($CDCl_3$) : 1.15 (3H, t), 2.70–3.40 (7H, m), 3.55–4.17 (2H, m), 4.83–5.15 (1H, m), 7.17 (1H).

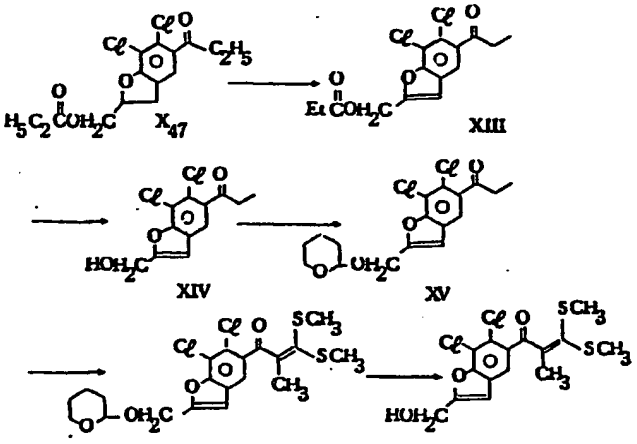
The compound X I_{47} (5.0 g, 18.2 mmol) is treated with 3.05g (36.3 mmol) of dihydropyrane in the same manner as in Example 44 to give 6.53 g (yield 100%) of the compound X II_{47}.

NMR δppm ($CDCl_3$): 1.18 (3H, t), 1.63 (6H, br), 2.73–4.17 (8H, m) 4.67 (1H, br), 4.93–5.40 (1H, m), 7.20 (1H).

The compound X II_{47} (4.0 g, 11.1 mmol) is allowed to react with 2.54 g (33.4 mmol) of carbon disulfide and 6.72 g (33.4 mmol) of 4-methoxybenzyl bromide in the same manner as in Example 46 to give the finally objective compound, which is recrystallized from water/isopropyl ether to give 0.060 g (yield 1.4%) of the compound I_{47} as pale yellow crystals, m.p. 85–87°C.

Anal. Calcd. (%) for $C_{14}H_{14}Cl_2O_3S_2$ 1/4H_2O
: C 45.47, H 3.95, Cl 19.18, S 17.34, H_2O 1.22,
Found (%) : C 45.54, H 3.94, Cl 19.18, S 17.38, H_2O 1.04.
IR νmax (Nujol) : 3360, 1685, 1603 cm $^{-1}$.
NMR δppm ($CDCl_3$) : [1.62 (d), 2.00 (s), 3H], [2.57 (s), 2.63 (s), 3H], 3.03–3.58 (3H, m), 3.70–3.95 (2H, m), 4.76–5.43 (1H, m).

Example 48
6,7-Dichloro-5-[2-methyl-3,3-bis(methylthio)propenoyl]-1-benzofuran-2-yl-methanol



In the same manner as in Example 33, 3.75 g (11.3 mmol) of the compound X_{47} (Example 47) is treated to give 2.95 g (yield 79.2%) of the compound X III.

NMR δppm ($CDCl_3$): 1.17, 1.22 (6H, t×2), 2.40 (2H, q), 2.93 (2H, q), 5.22 (2H, s), 6.78 (1H, s), 7.47 (1H, s).

In the same manner as in Example 33, 2.95 g (9.0 mmol) of the compound X III is treated to give 2.40 g (yield 98.0%) of the compound X IV as grayish white crystals, m.p. 93–95°C.

Anal. Calcd. (%) for $C_{12}H_{10}Cl_2O_3$
: C 52.77, H 3.69, Cl 25.96,
Found (%) : C 52.48, H 3.76, Cl 25.77.
IR νmax (Nujol) : 3250, 1704 cm $^{-1}$.

In the same manner as in Example 33, 2.20 g (8.1 mmol) of the compound X IV is treated with dihydropyrane to give 2.30 g (yield 79.9%) of the compound X V.

NMR δppm ($CDCl_3$): 1.22 (3H, t), 1.70 (6H, m), 2.95 (2H, q), 3.25–4.33 (2H, m), 4.50–5.00 (3H, m), 6.73 (1H, s), 7.45 (1H, s).

In the same manner as in Example 1, 2.10 g (5.9 mmol) of the compound X V is allowed to react for 18 hours to give 2.10 g (yield 77.2%) of the compound II_{48}.

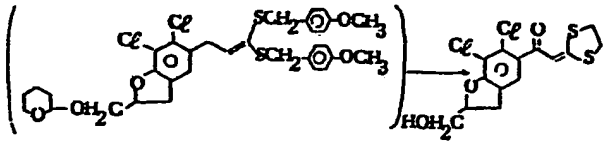
NMR δppm ($CDCl_3$): 1.67 (6H, m), 1.90 (3H, s), 2.27 (3H, s), 2.35 (1H, s), 3.33–4.17 (2H, m), 6.42 (3H, m), 6.73 (1H, s), 7.62 (1H, s).

In the same manner as in Example 44, 0.65 g (1.4 mmol) of the compound II_{48} is treated with anisole/trifluoroacetic acid to give 0.430 g (yield 80.8%) of the compound I_{48}, m.p. 120–122°C. This is recrystallized from isopropyl ether to give 0.352 g (yield 66.2%) of pale yellow crystals, m.p. 122–123°C.

Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_3S_2$: C 47.75, H 3.74, Cl 18.79, S 17.00,
Found (%) : C 47.63, H 3.81, Cl 18.65, S 16.88.
IR νmax (Nujol) : 3580, 3420, 1651, 1606 cm^{-1}.
NMR δppm ($CDCl_3$) : 1.88 (3H, s), 2.28 (3H, s), 2.35 (3H, s), 2.98 (1H, t), 4.75 (2H, d, D_2O, s), 6.62 (1H, s), 4.78 (1H, s).

Example 49

6,7-Dichloro-5-[2-(1,3-dithioran-2-ylidene)acetyl]-2,3-dihydro-1-benzofuran-2-yl-methanol



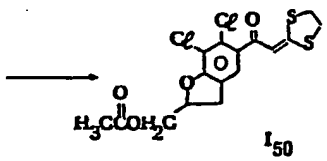
I_{49}

In the same manner as in Example 19, 1.0 g of the compound prepared from the 1st step of the processes in Example 47 is treated with 0.28 g of ethanedithiol to give 0.15 g (yield 11.2%) of the compound I_{49}, m.p. 165–170°C. This is recrystallized from ethyl acetate to give 0.10 g (yield 7.5%) of pale yellow crystals, m.p 170–171°C.

Anal. Calcd. (%) for $C_{14}H_{12}Cl_2O_3S_2$: C 46.28, H 3.33, Cl 19.52, S 17.65,
Found (%) : C 46.24, H 3.38, Cl 19.68, S 17.38.
IR νmax (Nujol) : 3410, 1605, 1590 cm^{-1}.
NMR δppm ($CDCl_3$) : 2.81 (1H, br-t), 3.07–4.25 (8H, m), 4.80–5.33 (1H, m), 6.93 (1H, s), 7.20 (1H).

Example 50

6,7-Dichloro-5-[2-(1,3-dithioran-2-ylidene)acetyl]-2,3-dihydro-1-benzofuran-2-yl-methanol acetate



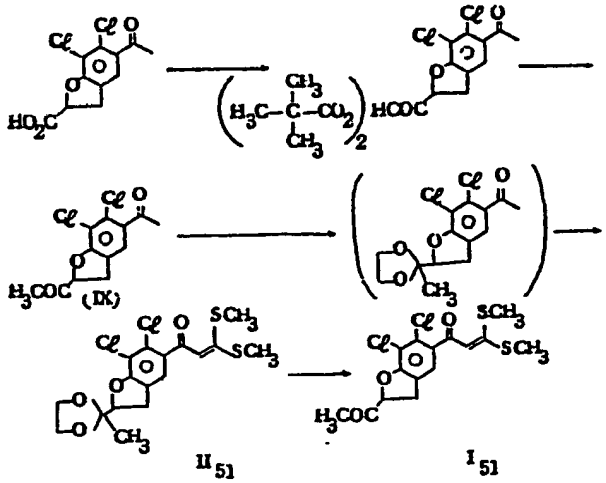
I_{50}

To a solution of 0.075 g (0.2 mmol) of the compound I_{49} (Example 49), 0.042 g (0.4 mmol) of triethylamine, and a catalytic amount of 4-(N,N-dimethylamino)-pyridine in 2 ml of dry dichloromethane is added 0.035 g (0.4 mmol) of acetyl chloride while being stirred under ice-cooling, and the mixture is allowed to react for 0.5 hour. The reaction product is chromatographed on a Lober column (type A) with benzene/ethyl acetate (10/1) as an eluent to give 0.08 g (yield 95.2%) of the compound I_{50}, m.p. 126–128°C. This is recrystallized from ether/ethyl acetate to give 0.05 g (yield 59.5%) of the compound I_{50} as grayish white crystals, m.p. 128–129°C.

Anal. Calcd. (%) for $C_{16}H_{14}Cl_2O_4S_2$
: C 47.41, H 3.48, Cl 17.50, S 15.82,
Found (%) : C 47.52, H 3.66, Cl 17.46, S 15.61.
IR νmax (Nujol) : 1726, 1738, 1638, 1620, 1605 cm^{-1}.
NMR δppm ($CDCl_3$) : 2.08 (3H, s), 2.95–3.72 (2H, m), 4.32 (2H, d), 4.98–5.43 (1H, m), 7.00 (1H, s), 7.28 (1H).

Example 51

1-,[6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-yl]-1-methyl ketone



II_{51} I_{51}

With thionyl chloride is treated 0.70 g (2.5 mmol) of 5-acetyl-6,7-dichloro-2,3-dihydro-1-benzofuran-2-carboxylic acid (W. F. Hoffman *et. al* J. Med. Chem., *24*, 865–873 (1981)) to give the corresponding acid chloride, the solution of which dissolved in ether is treated with 1.1 g (5.1 mmol) of t-butyl malonate in ether in the presence of 0.18 g (4.9 mmol) of sodium hydride. The reaction product is, without isolation and purification, allowed to react with 3 ml of trifluoroacetic acid at room temperature for an hour, and then the trifluoroacetic acid is removed by evaporation. To the residue is added 15 ml of toluene and the mixture is refluxed under heating for 2.5 hours. The product is chromatographed on a Lober column (type B) with benzene/ethyl acetate (10/1) as an eluent to give 0.32 g (yield 46.0%) of the compound IX.

NMR: 2.35 (3H, s), 2.63 (3H, s), 3.27–3.63 (2H, m), 5.12–5.40 (1H, m), 7.37 (1H).
IR νmax ($CHCl_3$): 1715, 1680, 1690, 1605 cm^{-1}.

A mixture of 1.50 g (5.5 mmol) of the compound IX, 5.0 ml of ethylene glycol, and a catalytic amount of p-toluenesulfonic acid in benzene is refluxed under heating for 2 hours, during which time the water generated is removed as azeotrope. The crude product (1.80 g) is treated, isolated and purified in the same manner as in Example 1 to give 0.180 g (yield 7.8%) of the compound II_{51} as an oil.

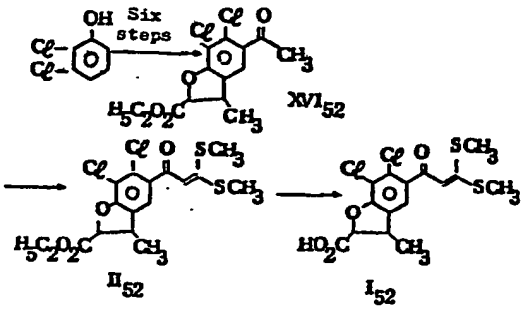
NMR δppm ($CDCl_3$): 1.37 (3H, s), [2.47 (s), 2.52 (s), 6H], 3.20–3.33 (2H, m), 4.00 (4H, br), 4.77–5.05 (1H, m), 6.47 (1H, s), 7.25 (1H).

The compound II_{51} (0.180 g, 0.4 mmol) is allowed to react with 2 ml of trifluoroacetic acid at room temperature for 6 hours to give 0.120 g (yield 74.8%) of the compound I_{51}, m.p. 98–101°C. This is recrystallized from ether/ethyl acetate to give 0.097 g (yield 59.6%) of grayish white crystals, m.p .102–103°C.

Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_3S_2$ $1/4H_2O$
: C 47.20, H 3.83, Cl 18.57, S 16.80, H_2O 1.18,
Found (%) : C 47.10, H 3.74, Cl 18.51, S 16.59, H_2O 1.00.
IR νmax (Nujol): 3420 (br), 1725, 1623, 1598, 1605 cm^{-1}.
NMR δppm ($CDCl_3$) : 2.33 (3H, s), 2.53 (6H, s), 3.30–3.60 (2H, m); 5.08–5.37 (1H, m); 6.43 (1H, s), 7.27 (1H).

Example 52

(2R, 3S/2S, 3R)-6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-3-methyl-2,3-dihydro-1-benzofuran-2-carboxylic acid



The starting material 2,3-dichlorophenol (made by Aldrich Chemical Co.) is allowed to react with crotyl bromide in place of allyl bromide in the same manner as disclosed in W. F. Hoffman *et al* J. Med. Chem. *24* 865 (1981) to give the compound X VI in 12.2% yield, m.p. 92–93°C.

NMR δppm ($CDCl_3$): 1.20–1.43 (6H, m), 2.62 (3H, s), 3.63–3.77 (1H, m), 4.28 (2H, q), 5.37 (1H, d, J=9.8Hz), 7.23 (1H).

In the same manner as in Example 1, 0.8 g (2.5 mmol) of the compound X VI is treated to give 0.187 g (yield 17.6%) of the compound II_{52}.

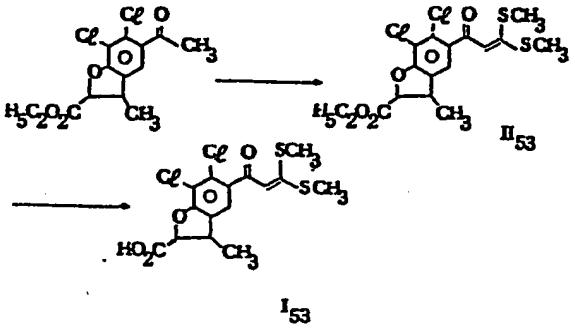
NMR δppm ($CDCl_3$): 1.17–1.43 (6H, m), 2.52 (6H, s), 3.48–4.45 (3H, m), 5.38 (1H, d, J=9.8Hz), 6.48 (1H, s), 7.28 (1H).

In the same manner as in Example 1, 0.187 g (0.4 mmol) of the compound II_{52} is hydrolyzed to give 0.174 g (qu. yield) of the compound I_{52}, m.p. 236–239°C. This is recrystallized from ethyl acetate to give 0.137 g (yield 77.4%) of pale yellow crystals, m.p. 236–239°C.

Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_4S_2$ $1/4H_2O$
: C 45.29, H 3.67, Cl 17.83, S 16.12, H_2O 1.13,
Found (%) : C 45.51, H 3.68, Cl 17.75, S 15.88, H_2O 1.00.

Example 53

(2R, 3R/2S, 3S)-6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-3-methyl-2,3-dihydro-1-benzofuran-2-carboxylic acid



In the same manner as in Example 52, 0.80 g (2.5 mmol) of the compound X VI_{53}:

NMR δppm ($CDCl_3$): 1.20–1.56 (6H, m), 2.63 (3H, s), 3.35–4.00 (1H, m), 4.30 (2H, q), 4.90 (1H, d, J=6.4Hz), 7.33 (1H).

which is obtained in Example 52 as the *trans* isomer (yield 12.5%) of the compound X VI_{52} (*cis* form), is treated to give 0.085 g (yield 8.0%) of the compound II_{53}.

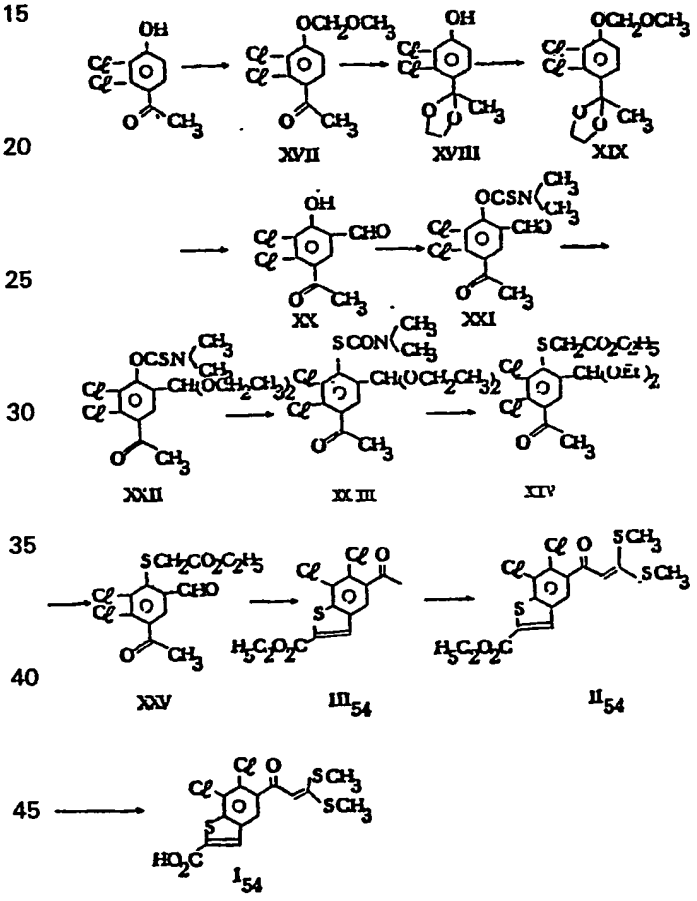
NMR δppm ($CDCl_3$): 1.17–1.53 (6H, m), 2.45 (3H, s), 2.56 (3H, s), 3.37–4.00 (1H, m), 4.25 (2H, q), 4.80 (1H, d, J=6.4Hz), 6.42 (1H, s), 7.17 (1H).

In the same manner as in Example 52, 0.085 g (0.2 mmol) of the compound X VI_{53} is hydrolyzed to give 0.079 g (qu. yield) of the compound I_{53}, m.p. 122–124°C. This is recrystallized from ether to give 0.050 g (yield 63.3%) of pale yellow crystals, m.p. 124–125°C.

Anal. Calcd. (%) for $C_{15}H_{14}CL_2O_4S_2$
: C 45.80, H 3.59, Cl 18.03, S 16.31,
Found (%) : C 45.64, H 3.70, Cl 18.13, S 16.21.

Example 54

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]benzo[b]thiophene-2-carboxylic acid



To 6.30 g (30.7 mmol) of 2,3-dichloro-4-hydroxybenzophenone [Sprague, James, M. (Merck) U.S. 345, 312] are added 8.5 g (61.5 mmol) of anhydrous powderly potassium carbonate and 63 ml of acetonitrile, and then 3.7 g (46.0 mmol) of chloromethyl methyl ether is added at room temperature while being stirred, and the resulting mixture is allowed to react for 3 hours. The unpurified reaction product is dissolved in 300 ml of benzene, and 5 ml of ethylene glycol and catalytic amount of p-toluenesulfonic acid are added, and the mixture is refluxed for continuous dehydration for 8 hours while being stirred to give 5.90 g of the compound X VIII, yield 77.1%, mp. 150–152°C.

NMR ($CDCl_3$) δppm: 1.78(3H,s), 3.57–3.90(4H, m), 5.83(1H, brs disappeared by addition of D_2O), 6.85–7.43(2H, d-d).

A mixture of 5.90 g (23.7 mmol) of the compound X VIII, 6.55 g (47.4 mmol) of anhydrous powderly potassium carbonate, 2.10 g (26.1 mmol) of chloromethyl methyl ether and 60 ml of acetonitril is allowed to react at room temperature for 2 hours while being stirred to give 6.60 g of the compound X IX, quantitative yield.

NMR ($CDCl_3$) δppm: 1.78(3H,s), 3.50(3H,m), 3.50–4.10a(4H,m), 5.25(2H,s), 7.02–7.50(2H,d-d).

In the same manner as disclosed in the literure [Holdor, Christensen, Synth. Comm. *5*(1), 65–78] is treated 6.60 g of the compound X IX to give 3.72 g of the compound X X, yield 67.5%. To a solution of 1.30 g (5.6 mmol) of the compound X X in 6.5 ml of N,N-dimethylformamide is added a suspension of 0.277 g (6.1 mmol) of 65 % sodium hydride in 3 ml of DMF over a 1/6 hour period, and then added 1.0 g (8.1 mmol) of dimethylthiocarbamoyl chloride (Made by Aldrich), and the resultant mixture is allowed to react at room temperature for 1/2 hours and then on an oil bath at 60–65°C for 2 hours.

The reaction product is treated with methanol to give 0.922 g of the compound X X I, yield 51.6 %, mp. 121–122°C.

NMR ($CDCl_3$) δppm: 2.63(3H,s), 3.38(6H,m), 7.65(1H,m), 9.92(1H,s).

To a solution of 1.70 g (5.3 mmol) of the compound X X I in 12 ml of dry ethanol are added 0.051 g (1 mmol) of aluminium chloride and 1.4 ml (8.5 mmol) of orthoethyl formate, and the mixture is refluxed for 2 hours while being stirred to give 2.10 g of the reaction product (yield qu). To this, without purification, is added 18 ml diphenyl ether and the mixture is allowed to react in nitrogen atmosphere on an oil bath at 225–230°C for 0.5 hour. Diphenyl ether is removed by evaporation under reduced pressure and the residue is chromatographed on 40 g of alumina to give 1.65 g of the compound X X III (yield 79.0 %)

NMR ($CDCl_3$) δppm: 1.20(6H,t), 2.62(3H,s), 3.12(6H,brs), 3.58(4H,qu), 5.77(1H,s), 7.73 (1H,s).

To a solution of 1.65 g (4.2 mmol) of the compound X X III in 33 ml of methanol is added 3.7 ml (9.3 mmol) of 10% sodium hydroxide in nitrogen atmosphere while being stirred. The mixture is refluxed under heating for 2.5 hours. The reaction mixture is evaporated to dryness. To a solution of the residue dissolved in 10 ml of acetonitril is added 0.55 ml (5.0 mmol) of ethyl bromoacetate in nitorgen atmosphere while being stirred, and the mixture is allowed to react at room temperature for 3 hours. The reaction mixture is chromatographed on a Lober column (Type B) with a benzene/ethyl acetate (10/1) to give 1.20 g of the compound X X IV, yield 69.9%.

NMR ($CDCl_3$) δppm: 1.62–1.35(9H, m), 2.62(3H,s), 3.48–4.25 (8H,m), 5.98(1H,s), 7.67(1H,s).

To 120 g (2.9 mmol) of the compound X X IV is added 3.6 ml of trifluoroacetice acid and the mixture is allowed to react for 1 hour in nitorgen atmosphere while being stirred. The reaction product is chromatographed on a Lober column (Type B) with benzene/ethyl acetate (10/1) as an eluent to give 0.650 g of the compound X X V, yield 66.0%.

NMR ($CDCl_3$) δppm: 1.17(3H,t), 2.63(3H,s), 3.70(2H,s), 4.08(2H,q), 7.72(1H,s), 10.75 (1H,s).

To 0.28 g (0.8 mmol) of the compound X X V is added 0.3 ml of 1N-soudim hydroxide at room temperature in nitorgen atmoshpere and the mixture is allowed to react for 1 hour (or in 1.4 ml of pyridine and 0.4 ml of pyperidine at 100–105°C for 1 hour.). The reaction product (0.27 g) is chromatographed on a Lober column (Type B) to give 0.150 g of the compound III_{34}, yield 56.6%.

NMR ($CDCl_3$) δppm: 1.42(3H,t), 2.67(3H,s), 4.08(2H,q), 7.87(1H,s), 8.02(1H,s).

The compound III_{54} (0.15 g, 0.5 mmol) is allowed to react in the same manner as in Example 1 to give 0.075 g of the compound II_{54}, yield 37.7%.

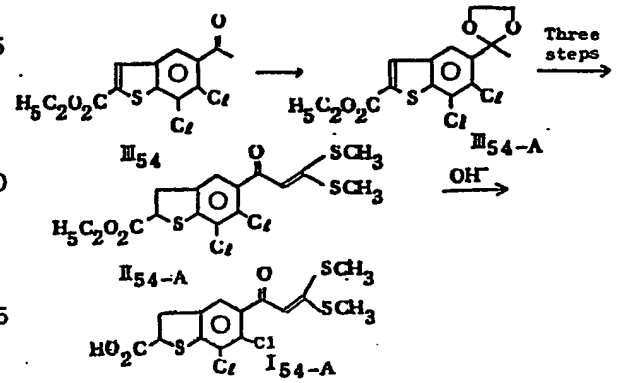
NMR ($CDCl_3$) δppm: 1.40(3H,t), 2.48(3H,s), 2.53(3H,s), 4.38(2H,q), 7.80(1H,s), 7.93(1H,s).

In the same manner as mentioned in Example 5 is hydrolyzed 0.075 g (0.2 mmol) of the compound II_{54} to give 0.066 g of the compound I_{54}, quantitative yield, mp. 223–225°C (dec.). This is recrystallized from ethyl acetate to give 0.038 g of grayish white crystals, yield 57.8%, mp. 225–227°C (dec.).

Anal. Calcd. (%) for $C_{14}H_{10}Cl_2O_3S_{31}/4H_2O$
: C 42.26, H 2.66, Cl 17.82, S 24.18, H_2O 1.13,
Found (%) : C 42.02, H 2.79, Cl 17.72, S 24.02, H_2O 1.00.

Example 54-A

6,7-Dichloro-5-[3,3-bis(methylthio)-2-propenoyl]-2,3-dihydro-benzo[b]thiophene-2-carboxylic acid



The mixture of 0.260 g (0.8 mmol) of the compound III_{54}, 1 ml of ethylene glycol, a catalytic amount of p-toluenesulfonic acid and 10 ml of benzene is refluxed for 48 hours while being stirred, during which time the water produced is removed continuously. The reaction mixture is cooled, poured into a mixture of ammonia water and ice and extracted with benzene. The organic layer is washed tiwce with water, dried over anhydrous magnesium sulfate and the benzene is removed to give 0.280 g of the compound $III_{54\ A}$, yield 88.0%, mp. 114–116°C.

NMR δppm ($CDCl_3$): 1.42 (3H, t), 1.83(3H,s), 3.53–4.38 (6H,m), 7.92(1H,s), 8.0(1H,s).

To 0.280 g (0.8 mmol) of the compound $III_{54\ A}$ are added 5 ml of dioxane and 5 ml of 1N-sodium hydroxide, and the mixture is allowed to react for 3 hours at room temperature and then evaporated. To a solution of the residue dissolved in 10 ml of water is added sodium amalgam (perpared from 33 mg of sodium and 1.3 mg of mercury) in small portions over a 30 minute period and the mixture is allowed to react for further 6 hours. The precipitate is removed and resulting alkaline solution is acidfied (pH 3–4) with 10% hydrochloric acid. This solution is extracted three times with ether. The organic layer is washed with water, dried over anhydrous magnesium sulfate and evaporated to give residue, to which are added 10 ml of ethanol and a catalytic amount of conc. sulfuric acid. The mixture is refluxed for 4 hours while being stirred. The reaction product (0.20 g) without purification is allowed to react in the same manner as in Example 1 and chromatographed on a Lober column (Type A) with ethyl acetate/benzene (1.15) as an eluent to give 0.04 g $II_{54\ A}$, yield 12.2%.

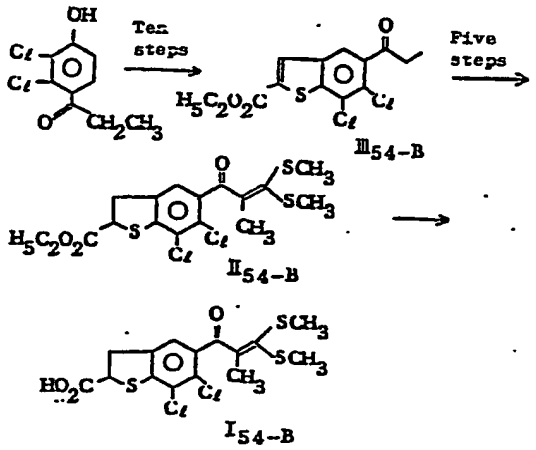
NMR δppm ($CDCl_3$): 1.28(3H, t), 2.52(3H, s), 2.55(3H, s), 3.50–3.85(2H, m), 4.20(2H, q), 4.37–4.60(1H, m), 6.60(1H, s), 7.63 (1H).

The compound $II_{54\ A}$ (0.04 g, 0.1 mmol) is hydrolyzed with an alkali to give the compound $I_{54\ A}$ in quantitative yield, mp. 170–173°C. This is recrystallized from ether to give 0.02 g of yellow crystals, mp. 173–174°C, yield 53.5%.

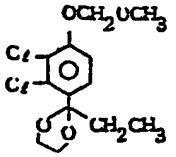
Anal. Calcd. (%) For $C_{14}H_{12}Cl_2O_3S_3$
: C 42.53, H 3.06, Cl 17.94, S 24.33,
Found (%) : C 42.41, H 3.01, Cl 18.15, S 24.51.

Example 54-B

6,7-Dichloro-5-[2-methyl-3,3-bis(methylthio)propenoyl]-2,3-dihydro-benzo[b]thiophene-2-carboxylic acid



A strating material, 2,3-dichloro-4-hydroxy-propiophenone, is allowed to react in the same manner as in Example 54 to yield the compound III_{54-B}, which is allowed to react in the same manner in as Example 54-A to yield I_{54-B}. The yield and physical constants of intermediates are listed as follows.

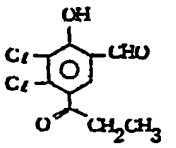


XIX B

70.0%

NMR : 0.87(3H, t) 2.15(2H, q)
3.52(3H, s) 3.62~4.18(4H, m)
5.25(2H, s) 6.95~7.55(2H, d-d)

↓

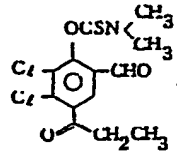


XX

85.0%

NMR : $\overset{CDCl_3}{ppm}$ 1.20(3H, t)
2.93(2H, q) 7.63(1H)
9.90(1H, s) 11.73(1H, br)
IR : $\nu_{max}^{CHCl_3}$ 3480, 3250(br)
1695(sh) 1660, 1603

↓

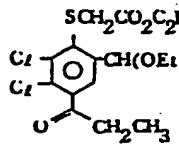


XXI B

58.5%

NMR : $\overset{CDCl_3}{ppm}$ 1.22(3H, t)
2.95(2H, q) 3.45(6H, s)
7.78(1H, s) 9.95(1H, s)

↓

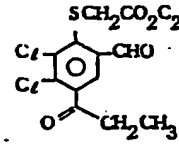


XXIV B

46.2%

NMR : $\overset{CDCl_3}{ppm}$ 1.05~1.35(12H, m)
2.90(2H, q) 3.47~3.82(4H, m)
4.05(2H, q) 5.95(1H, s)
7.53(1H, s)

↓



XXV-B

79.4%

NMR : $\overset{CDCl_3}{ppm}$ 1.23, 1.42(6H, t×2) 2.96(2H, q) 4.08(2H, q)
4.00(2H, s) 7.58(1H, s)
10.67(1H, s)

Compound III_{54-B}: yield 0.680 g (yield 96.4%), mp. 98–99°C.

NMR δppm ($CDCl_3$): 1.12–1.55(6H,m), 2.97(2H,q), 4.42(2H,q), 7.75(1H,s), 7.98 (1H,s).

Compound II_{54-B}: (yield 7.4%)

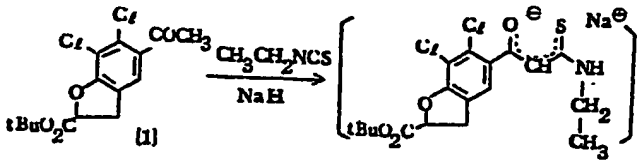
NMR δppm ($CDCl_3$): 1.28(3H,t), 2.08(3H,s), 2.15(3H,s), 2.35(3H,s), 3.40–3.93(2H,m), 4.00–4.63(3H,m), 7.57(1H).

Compound I_{54-B}: (yield 91.2%), mp. 131–132°C.

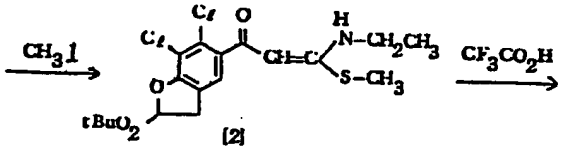
Anal. Calcd. (%) for $C_{15}H_{14}Cl_2O_3S_3$
: C 44.01, H 3.45, Cl 17.41, S 23.50,
Found (%): C 44.05, H 3.24, Cl 17.35, S 23.41.

Example 55

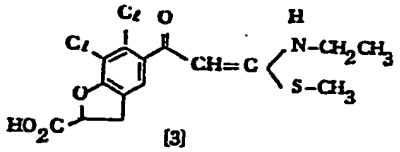
Preparation of 6,7-dichloro-5-(3-ethylamino-3-methylthio-2-propenoyl)-2,3-dihydro-benzofuran-2-carboxylic acid [3]



[1]



[2]



[3]

[Step-1]

A solution of 1.65 g (5 mmol) of tert-butyl 6,7-dichloro-5-acetyl-2,3-dihydro-benzofuran-2-carboxylate [1] in 4 ml of dry dimethylformamide is added to a mixture of 0.20 g (5 mmol) of 60% oily sodium hydride, 0.53 g (6 mmol) of ethyl isothiocyanate and 1 ml of DMF in nitrogen atmosphere at 5–10°C while being stirred, and the resultant mixture is kept at the same temperature of 2.5 hours. To the reaction mixture is added 0.85 g (6 mmol) of methyl iodide and the mixture is allowed to react for 2.5 hours. After addition of an ammonium chloride solution, the mixture is extracted with ether. The organic layer is washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and then evaporated under reduced pressuer. The residue is isolated and purified by medium pressure column chromatography on silica gel to give 1.6 g of the compound [2] as an oil, yield 76.5%.

IR: νmax ($CHCl_3$) 1750 (CO–O), 1609(sh)-1565(br) (aminopropenoyl portion) cm^{-1}.
NMR δppm ($CDCl_3$): 10.4(1H,br), 7.12(1H,s), 5.26(1H,s), 5.18(1H,d-d), 3.80–3.32(4H,m), 2.39(3H,s) 1.49, 1.32(12H,s+t).

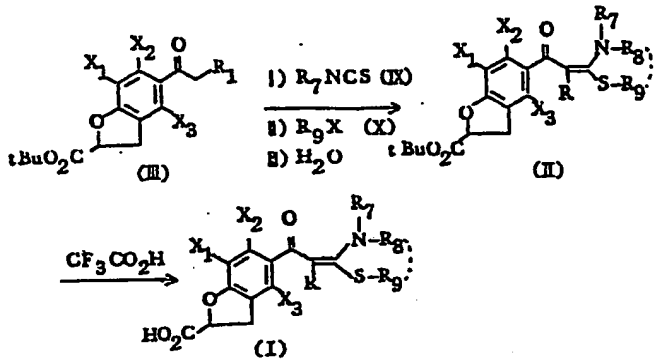
[Step-2]

To 1.3 g of the compound [2] perpared in Step-1 is added 13 ml of trifluoroacetic acid and the mixture is stirred for 0.5 hour at room temperture. Trifluoroacetic acid is removed under reduced pressure to give residue which is crystallized from a small amount of ether. The resulting crystals are collected by filtration and washed with a small amount of ether to give 1.15 g of the titled compound [3]. This is recrystallized from acetone to give 0.81 g of yellowish white crystals, yield 69.8% (Yield from compound [1] is 53.4%), mp. 247–249°C (dec.).

Anal. Calcd. (%) for $C_{15}H_{15}Cl_2NO_4S$
: C 47.88 H 4.02, Cl 18.85, N 3.72,
Found (%): C 47.76, H 3.90, Cl 19.03, N 3.80.

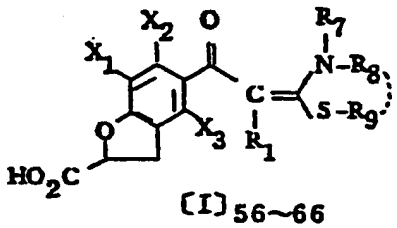
IR: νmax (Nujol) 3300–2200(br) 2200–1800(br) 1735, 1610, 1565 cm^{-1}.
NMR δppm (DMSO d-6): 11.30(1H,br), 7.29(1H,s), 5.41(1H, d-d), 5.21(1H,s), 3.80–3.20(4H,m), 2.42(3H,s), 1.23(3H,t).

Example 56–66



The compound (III) is allowed to react with the compound IX (1.2 equiv. mole) in a solution of 60% oily sodium hydride (equiv. mole) in DMF or dimethylacetoamide (DMA) and tetrahydrofuran (THF) under nitrogen atmoshere at 5–15°C, then, the compound (X) is added thereto, and the mixture is allowed to react at a temperature of 5°C to room temperature. Ammonium chloride is added to the reaction mixture and the resulting mixture is extracted with ether. The ether residue is purified by column chromatography on silica gel to give the compound (II) which is allowed to react with 10 equivalent amount of trifluoroacetic acid at room temperature for 0.5–1.0 hour. The reaction mixture is evaporated under reduced pressure and the residue is crytallized from ether to give the aimed compound [I]. The compound [I] is recrystallized from an appropriate solvent as occasion demands for the porpose of further purification. The respective examples are shown in table 5 (Nos. 1–4).

Table 5 (No. 1)



〔I〕56~66

Example Nos.	X_1~X_3	R_1	R_7	R_8	R_9	Yield (from Ⅲ) (%)
56	6,7-di-Cℓ	H	CH_3	H	CH_3	44.6
57	〃	H	CH_3	H	C_2H_5	39.5
58	〃	H		H	CH_3	62.1
59	〃	CH_3	C_2H_5	H	CH_3	67.5
60	〃	CH_3	CH_3	H	CH_3	60.3
61	〃	H	CH_3	H	$-CH_2-CH=CH_2$	46.7
62 -1)	〃	H	CH_3	$-CH-(OCH_3)-CH_2$		29.4
63 -2)	〃	H		$-CH_2-CH_2-$		34.6
64 -3)		H	Me	$-\overset{O}{\overset{\|}{C}}-CH_2-$		60.5
※ 65	X_1=Me X_3=Cℓ	H	Me	H	Me	21.7
※ 66	X_1=Me X_2 X_3=H	H	Me	H	Me	6.2

※ Starting materials were prepared according to the method of William F. Hoffman et al. J. Med. Chem. (1981) 24 865~873

-1) $R_9X=BrCH_2CH\langle^{OMe}_{Br}$ -2) $R_9X=BrCH_2CH_2Br$ -3) $R_9X=BrCH_2CO_2Et$

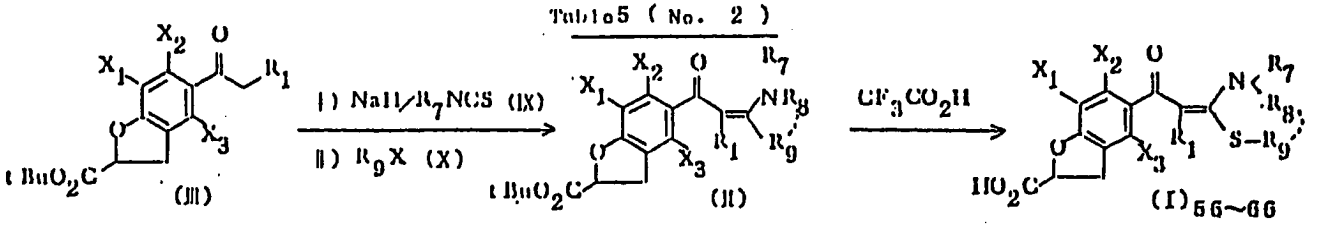
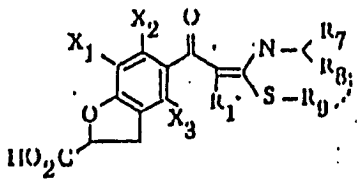


Table5 (No. 2)

Example Nos.	Amount Used (III) Compd	Solvent(ml)	Reaction Temp.	Time	Compds (X) R_9X	Reaction Temp.	Time	Yield of (II) (%)	Yield of (I) (%)
56	0.994(3)	DMF (4)	5~10°	2	MeJ	5~r.t.	1	57.3	77.8
57	〃	〃	〃	1	EtJ	〃	1	46.0	85.9
58	1.65 (5)	〃 (6)	〃	2	MeJ	〃	1	70.8	87.7
59	1.04 (3)	〃 (4)	〃	2	MeJ	〃	1	77.6	87.0
60	1.04 (3)	DMF—THF (1:3)	〃	2	MeJ	〃	1	62.2	96.9
61	0.994(3)	DMF—THF (〃)	〃	2	CH_2=CH-CH_2Br	r.t.	2	51.0	91.5
62	1.32 (4)	DMF—THF (〃)	5~8°	3	 -a)	-50~-10°	2	40.7	72.3
63	0.994(3)	DMF—THF (〃)	5~10°	2	BrCH_2CH_2Br -a)	5~r.t.	18	61.0	56.7
64	0.994(3)	DMF—THF (〃)	〃	2	BrCH_2CO_2Me	5~15°	1.5	62.0	97.5
65	0.90 (3)	DMF (4)	〃	2	MeJ	〃	1	22.7	95.6
66	1.38 (5)	DMF (6)	5~25°	1	MeJ	〃	1	7.7	80.1

-a) Equivalent mole of NaH is added

Table 5 (No. 3)



(I)

Example Nos.	Recrystallized from	m.p. (℃)	Molecular formula	Elementary Analysis									
				Calcd.					Found				
				C	H	Cℓ	N	S	C	H	Cℓ	N	S
56	DMF – ethanol	263~265 (d)	$C_{14}H_{13}Cℓ_2NO_4S$	46.40	3.62	19.57	3.87	8.85	46.44	3.70	19.32	3.96	8.66
57	〃	249~251 (d)	$C_{15}H_{15}Cℓ_2NO_4S$	47.88	4.02	18.84	3.72	8.52	47.79	4.04	18.57	3.82	8.30
58	acetone	223~225 (d)	$C_{19}H_{15}Cℓ_2NO_4S$	53.78	3.63	16.71	3.30	7.55	53.93	3.83	16.49	3.15	7.70
59	acetone	194~196 (d)	$C_{16}H_{17}Cℓ_2NO_4S$	49.24	4.39	18.17	3.59	8.21	49.12	4.45	18.28	3.59	8.48
60	DMF – water	206~207 (d)	$C_{15}H_{15}Cℓ_2NO_4S$	47.88	4.02	18.85	3.72	8.52	47.66	4.00	18.56	3.88	8.44
61	ethanol	178~180 (d)	$C_{16}H_{15}Cℓ_2NO_4S$	49.50	3.89	18.26	3.61	8.26	49.44	3.86	18.33	3.64	8.10
62	ethanol	258~260 (d)	$C_{16}H_{15}Cℓ_2NO_5S$	47.53	3.74	17.54	3.47	7.93	47.40	3.90	17.84	3.59	7.80
63	ethanol	225~228 (d)	$C_{20}H_{15}Cℓ_2NO_4S$ $\frac{1}{3}-C_2H_5OH$	54.78	4.39	14.70	2.90	6.65	54.42	4.35	15.05	3.03	6.60
64	ethanol	253~256 (d)	$C_{15}H_{11}Cℓ_2NO_5NS$	46.41	2.86	18.26	3.61	8.26	41.31	2.96	18.12	3.54	8.07
65	ethanol	248~250 (d)	$C_{15}H_{16}Cℓ NO_4S$	52.71	4.72	10.37	4.10	9.38	52.66	4.89	10.04	4.03	9.17
66	ethanol	210~220 (d)	$C_{15}H_{17}NO_4S$	58.62	5.57		4.56	10.43	58.30	5.67		4.61	10.21

Table 5 (No. 4)

Example Nos.	IR (ν_{max}^{Nujol} cm^{-1})	NMR (δ_{ppm}^{DMSO})
56	3200~2300, 2100~1800, 1730, 1569	11.15(1H,br) 7.30(1H,s) 5.42(1H,d-d) 5.22(1H,s) 3.85~3.20(2H,m) 3.0(3H,d) 2.43(3H,s)
57	3200~1800(br), 1735, 1610, 1570	11.2(1H,br) 7.28(1H,s) 5.42(1H,d-d) 5.25(1H,s) 3.85~3.15(2H,m) 3.1~2.9(5H,m) 1.29(3H,t)
58	3200~1800(br), 1738, 1608, 1592, 1530	13.03(1H,br) 7.38(6H,m) 5.53(1H,s) 5.42(1H,d-d) 3.85~3.10(2H,m) 2.40(3H,s)
59	3200~1800(br), 1741, 1608, 1570	(和t-Bu ester) 12.03(1H,br) 6.93(1H,s-like) 5.18(1H,d-d) 3.8~3.2(4H,m) 2.39(3H,s) 1.87(3H,s) 1.48(9H,s)
60	3200~1800(br), 1725, 1610, 1565	12~11(1H,br) 7.08(1H,s) 5.45(1H,d-d) 3.85~3.16(1H,m+s) 2.42(3H,s) 1.80(3H,s)
61	3200~1800(br), 1728, 1565	11.20(1H,br) 7.26(1H,s) 6.1~5.85(1H,m) 5.5~5.1(4H,m) 3.83~3.2(4H,s) 3.0(3H,d)
62	3200~1800(br), 1730(br), 1608, 1523	7.27(1H,s-like) 5.56~5.2(3H,s-like) 3.82~3.0(10H,m)
63	3140(br)~1800(br), 1728, 1600, 1490	7.45~7.19(6H,m) 5.09(1H,s) 5.42(1H,d-d) 4.10(2H,t) 3.8~3.2(8H,m) 1.06(3H,t)
64	~2580, 1763, 1732, 1600, 1570	7.40(1H,s) 6.46(1H,s) 5.49(1H,d-d) 3.90~3.17(7H,m)
65	3140(br)~1800(br), 1712, 1567, 1500	7.28(1H,s) 5.38(1H,d-d) 5.22(1H,s) 3.80~3.15(2H,m) 3.0(3H,d) 11.35(1H,br) 2.43(3H,s) 2.23(3H,s)
66	3200~2200, ~1950(br), 1732, 1570	11.50(1H,br) 7.10(2H,br) 5.06(1H,s) 5.27(1H,d-d) 3.80~3.10(2H,m) 2.98(3H,d) 2.50(3H,s) 2.20(3H,s)

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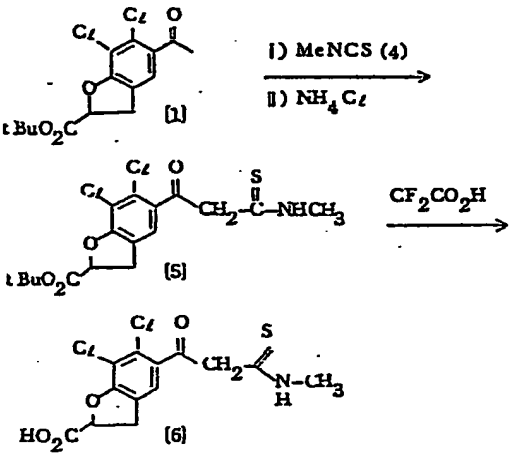
Example 67

Preparation of 6,7-dichloro-5-[[N-methyl(thiocarbamoyl)]-acetyl]-2,3-dihydrobenzofuran-2-carbaxylic acid [6]



[1] [5] [6]

The compound [1] (0.993·g, 3 mmol) is allowed to react with methyl isothiocyanate [4] in the same manner as in Example 56. To the resulting solution of the sodium salt [5] is added a saturated ammonium chloride solution and the mixture is extracted with ether. The organic layer is washed with a saturated solution of sodium chloride, dried over anhydrous magnesium salfate, and evaporated. The residue is chromatographed on silica gel to give 0.65 g of the compound [5] as a resinous product. (By IR and NMR spectra, the compound [5] is comfirmed as a mixture of keto-form and enol-form)

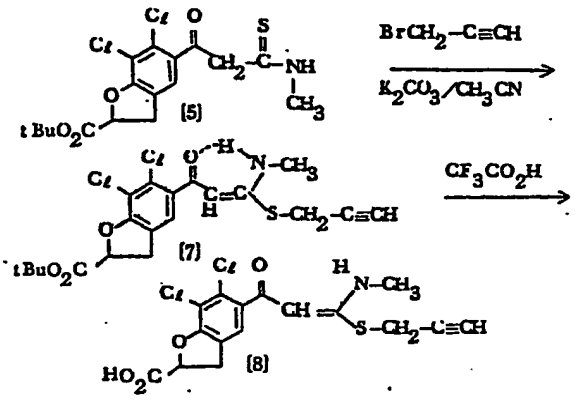
IR: νmax ($CHCl_3$) 3400(NH), 3330(br: hydrogen bond –OH), 1750(COO), 1683(CO–N–), 1620, 1610 cm $^{-1}$.
NMR δppm ($CDCl_3$): (Keto+enol mixture) 14.45(0.5H, brs), 8.9(0.5H, br), 5.60(0.5 H, s), 4.39(1H,s), 3.8–3.1(5H,m), 1.49(9H,s).

A mixture of 0.65 g (1.61 mmol) of the compound [5] with 6.5 ml trifluoroacetic acid is stirred for 0.5 hour at room temperature. The reaction mixture is treated in the same manner as in Example 56 and the product is recrystallized from benzene to give 0.34 g of the titled compound [6], yield 60.7 %, mp. 121–124°C.

Anal. Calcd. (%) for $C_{13}H_{12}Cl_2NO_4S$
: C 44.84 H 3.18, Cl 20.36, N 4.02, S 9.21,
Found (%): C 44.92, H 3.29, Cl 20.14, N 4.10, S 8.96.
IR: νmax(Nujol) 3240, 3400–2400(br), 1725, 1615, 1535cm $^{-1}$.
NMR δppm (DMSO d-6) [a mixture of the keto-form and enol(thiol)-form (1/2)]: 14.3(2/3H,br), 10.2–9.83(1H,br), 7.4–7.66(1H), 5.82(2/3H,s), 4.30(2/3H,s), 4.0–3.20(2H,m), 3.0(3H,d).

Example 68

Preparation of 6,7-dichloro-5-(3-methylamino-3-propargylthio-2-propenoyl)-2,3-dihydrobenzofuran-2-carboxylic acid [8]



A mixture of 0.3 g (0.74 mmol) of the compound [5] prepared in Example 67, 0.097 g (0.82 mmol) of propargyl bromide, 150 mg of dry potassium carbonate powder and 6 ml of dry acetonitrile is stirred at room temperature for 2 hours. The reaction mixture is concentrated under reduced perssure, and the residue is extracted with ether. The organic layer is washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue is purified by column chromatography on silica gel to give 0.30 g of the titled compound tert-butyl ester [7] as a resinous product, yield 91.6%.

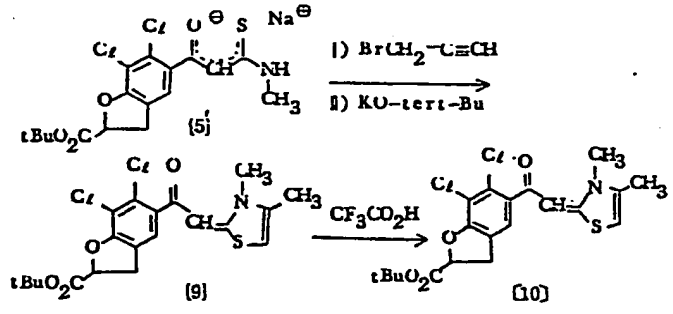
IR: νmax($CHCl_3$) 3320(acetylenic hydrogen), 1748, 1573 cm^{-1}.
NMR δppm ($CDCl_3$): 11.45(1H,br), 7.20(1H), 5.44(1H,s), 3.64(2H,d), 3.8–3.2(2H,m), 3.06(3H,d), 2.32(1H,m), 1.48(9H, s).

Subsequently, 0.61 g (1.38 mmol) of the compound [7] is allowed to react in the same manner as in Example 55 Step-2, and worked up and is recrystallized from ethanol to give 0.37 g of the titled compound, yield 69.5 %, mp. 180–183°C (dec.).

Anal. Calcd. (%) for $C_{16}H_{13}Cl_2O_4NS$
: C 49.75 H 3.39, Cl 18.36, N 3.63, S 8.30,
Found (%): C 49.50, H 3.58, Cl 18.51, N 3.57. S 8.15.
IR: νmax (Nujol) 3260(acetylenic hydrogen), -2500-(br)-1950(br), 1725, 1572 cm^{-1}.
NMR δppm (DMSO d-6): 11.16(1H,br), 7.30(1H,sbr), 5.40–5.42(2H,s,d-d), 3.90(2H,d), 3.70–3.20(3H,m), 2.99(3H,d).

Example 69

Preparation of 6,7-dichloro-5-[(3,4-dimethyl-4-thiazolin-2-yliden)acetyl]-2,3-dihydro-benzofuran-2-carboxylic acid [10]



In the same manner as in Example 67, a mixture of 0.993 g (3 mmol) of the compound [1], 0.12 g (3 mmol) of 60% oily sodium hydride and 0.263 g (3.6 mmol) of methyl isothiocyanate in DMA-THF (1/3) is allowed to react at 5–10°C for 2 hours. To the resulting sodium salt [5] is added 0.29 ml (3.6 mmol) of propargyl bromide. The mixture is allowed to react at 10°C to room temperature for 3 hours, then, 0.07 g (0.6 mmol) of tert-butoxide is added thereto, and the resulting mixture is allowed to react at room temperature overnight. Saturated ammoniun chloride solution is added and the mixture is extracted with ether. The ether extract is purified by column chromatography on silica gel and crystallized from a small amount of ether to give 0.50 g of the compound [9], yield 37.7%, mp. 152–153°C.

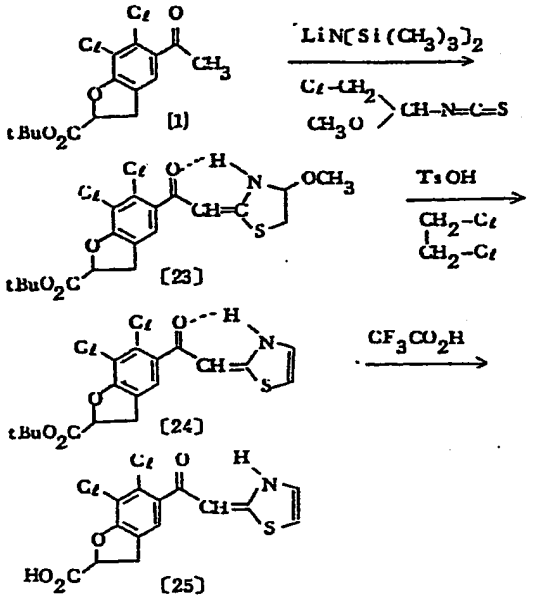
IR: νmax ($CHCl_3$) 1750, 1604, 1563, 1482 cm^{-1}.
NMR δppm ($CDCl_3$): 7.33(1H,s-like), 6.18(1H,s-like), 6.04(1H,s), 5.20(1H,d-d), 3.8–3.20+3.46(s)(6H), 2.26(3H,s), 1.49(3H,s).

In the same manner as in Example 55 (Step-2), 0.8 g of the compound [9] is allowed to react and worked up, and the product is recrystallized from DMF-ethanol to give 0.6 g of the titled compound, yield 85.9%, mp. 277–279°C (dec.).

Anal. Calcd. (%) for $C_{16}H_{13}Cl_2O_4NS$
: C 49.75, H 3.39, Cl 18.36, N 3.63, S 8.30,
Found (%): C 49.51, H 3.61, Cl 18.09, N 3.78. S 8.04.
IR: νmax (Nujol) 3120, -2480-(br), 1740(br), 1663, 1513cm $^{-1}$.
NMR δppm (DMSO, d-6): 6.00(1H,s), 5.44(1H,d-d), 3.85–3.3(5H, m+s), 2.26(3H,s).

Example 70

Preparation of 6,7-dichloro-5-[(4-thiazolin-2-ylidene)acetyl]-2,3-dihydro-benzofuran-2-carboxylic acid [25]



A solution of 1.99 g (6 mmol) of the compound [1] in 6 ml of dry tetrahydrofuran (hereinafter abbreviated to as THF) is added to a solution of hexamethyl disilazane lithiumamine prepared from 1.3 ml (6.3 mmol) of hexamethyl disilazane and 4.2 ml (6.3 mmol) of a hexane solution of n-butyl lithium (1.5 N) at −78°C. The mixture is allowed to react at −70 to −78°C for 0.5 hour and a solution of 1.0 g (6.6 mmol) of 2-chloro-1-methoxy ethyl isothiocyanate [22]* in 2 ml of THF is added thereto. The temperature of the reaction mixture is raised slowly and kept at 5–7°C for 3 hours, further at 10–15°C for 2 hours, and then, an ammonium chloride solution is added thereto. The resulting mixture is extracted with ether and the organic layer is a washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated at below 0°C under reduced pressure. The residue is chromatographed on silica gel to give a mixture of the compound [23] and the strating material. The mixture is dissolved in 10 parts by volume of dichloromethane and 50 mg of anhydrous p-toluenesulfonic acid (hereinafter abbreviated to as p-TsOH) is added thereto. The mixture is heated under refluxing for 10 minutes, then, after cooling, washed with sodium dicarbonate, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue is purified by chromatography on silica gel to give 0.85 g (42%) of the starting material and 0.78 g of the objected compound [24], yield 31.3%.

IR: νmax ($CHCl_3$) 1750–1700(br), 1630, 1607 cm^{-1}
NMR δppm ($CDCl_3$): 7.72(d), 7.66(d), 7.4–7.23(m), 7.07(d), (total 3H) 6.10(s), 4.68(s) 5.2(1H,m) 3.8–3.2(2H,m) 1.50(9H, s) [NMR spectra indicated that the product was a mixture of thiazolin-form and thiazol-form in a solution.]

In the same manner as in Example 55 Sept-2, 0.75 g of the compound [24] is allowed to react and treated to give 0.60 g of the titled compound. Crystallized from acetone, and subsequent recrystallization from ethanol gave 0.3 g of the crystals, yield 46.3%, (yield from [1] 14.5%), mp. 214–216°C.

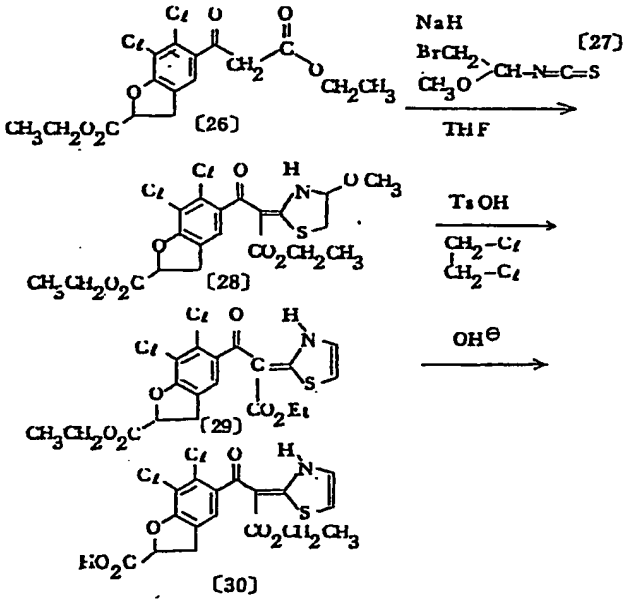
Anal. Calcd. (%) for $C_{14}H_{19}Cl_2NO_4S$
: C 46.94 H 2.53, Cl 19.80, N 3.91, S 8.95.
Found (%): C 46.85, H 2.70, Cl 19.95, N 3.96, S 8.87.
IR: νmax (Nujol) 2800–2000, 2000–1800, 1715, 1683 cm^{-1}.
NMR δppm (DMSO d-6): 7.8–7.1(3H,m) 6.13(s,0.75H) 5.45(1H, m), 4.75(0.5H,br), 3.85–3.2(2H,m). [a mixture of 75% thiazolin-form and 25% thiazol-form]

* The compound [22] can be synthesized as follows.
A mixture of 4 g (32 mmol) of chlorodimethylacetal and 4.4 g (16.8 mmol) of silicon tetraisothiocyanate [$Si(NCS)_4$] is allowed to react at 80–85°C for 6 hours. The reaction mixture is poured into ice and extracted with ether. The ether layer is washed with a sodium dicabonate solution, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue is distilled to give 4.34 g of the compound [22], yield 90.5%, bp. 92–93°C (28 mmHg)

IR: νmax (CCl_4) 2000(br) cm^{-1} (N=C=S) cm^{-1}.

Example 71

Preparation of 6,7-dichloro-5-[2-(4-thiazolin-2-ylidene)-2-(carbethoxy)acetyl]-2,3-dihydro-benzofuran-2-carboxylic acid [30]



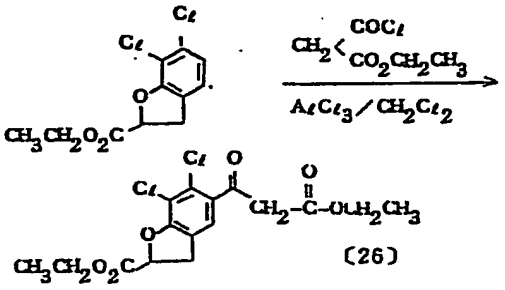
A solution of 1.0 g (2.67 mmol) of the compound [26] in 3 ml of a mixture of dimethylacetamide (hereinafter abbreviated to as DMA) and THF (1/3) is added to a solution of 0.107 g (2.67 mmol) of 60% oily sodium hydride in 1 ml of DMA-THF (1/3) at 5–7°C in nitrogen atmosphere. The mixture is stirred for 15 minutes, and 0.575 g (2.95 mmol) of the compound [27] is added thereto at −30°C. The mixture is kept at 0–10°C for 3 hours, then at 5°C overnight, and then at 20–25°C for 3 hours. The reaction mixture is worked up in the same manner as in Example 70 to give 0.86 g of the compound [28], yield 65.6%. Further, this is treated with p-TsOH in the same manner as in Example 70 to give 0.773 g of the compound [29], yield 96.3% (yield from the compound [26], 63%)

IR: νmax ($CHCl_3$) 3280(bs), 1755, 1738, 1645(br), 1610, 1561, 1540 cm^{-1}.
NMR δppm ($CDCl_3$): [15.5(br)+13.3(br)](1H), 7.4(1H,br), 7.0(2H,br+s), 5.30(1H, d-d), 4.4–3.2(6H,m), 1.30(3H,t), 0.86(3H,t).

The compound [29] is hydrolyzed with NaOH to give 0.4 g of the titled compound [30], yield 58.5%. This is recrystallized from acetone to give crystalls having mp. 212–215°C.

Anal. Calcd. (%) for $C_{17}H_{13}Cl_2NO_6S$
: C 47.46 H 3.05, Cl 16.48, N 3.25, S 7.45,
Found (%): C 47.47, H 3.33, Cl 16.34, N 3.22, S 7.18.
IR: νmax (Nujol) 3150, 3120, 1727, 1644 cm^{-1}.
NMR δppm (DMSO d-6): 13.7(1H,br), 7.16(1H,d), 7.28(1H,d), 7.04(1H,s-like), 5.40 (1H,d-d), 3.9–3.15(5H,m), 0.73(3H,t).

○ The strating compound [26] is synthesized as follows.



(26)

A mixture of 2.6 g (10 mmol) of ethyl 6,7-dichloro-2,3-dihydro-benzofuran-2-carboxylate, 1.96 g (13 mmol) of ethylmalonyl chloride, 4.8 g (36 mmol) of anhydrous aluminium chloride and 30 ml of dry dichloromethane is allowed to react at room temperature overnight and then poured into water. The resulting mixture is extracted with dichloromethane, and the organic layer is washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue is chromatographed on silica gel to give 0.75 g of the objected compound [26], yield 20% and 0.81 g of the starting material (31%).

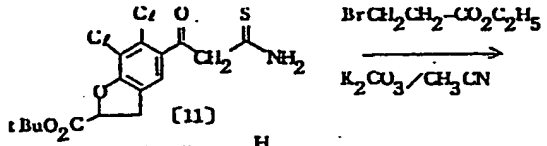
IR: νmax (CCl_4) 1765, 1743, 1650–1628(br), 1610 cm^{-1}.
NMR δppm ($CDCl_3$): 7.40(1H,s-like), 5.45(0.5H,s), 5.3(1H,m), 4.9–3.25(7H,m), 1.4–1.15(12H,s,t), [a mixture of keto-enol forms (1/1)].

Further the reagent [27] can be synthesized from bromodimethylacetal in the same manner as the compound [22] mentioned in Example 70, yield 85%, bp. 86–86°C (10 mmHg).

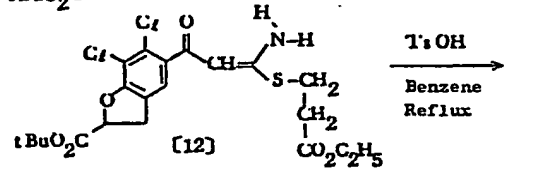
IR: νmax (CCH_4) 2000 cm^{-1} (br) (N=C=S) cm^{-1}.

Example 72

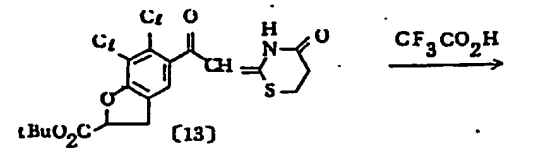
Production of 6,7-dichloro-5-[(4-oxo-perhydro-1,3-thiazin-2-ylidene)acetyl]-2,3-dihydro-benzofuran-2-carboxylic acid [14]



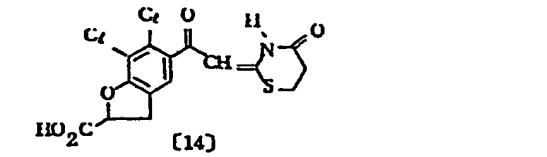
(11)



(12)



(13)



(14)

STEP 1

A mixture of 0.39 g (1mmol) of t-butyl 6,7-dichloro-5-[(thiocarbamoyl)acetyl]-2,3-dihydrobenzofuran-2-carboxylate, 0.21 g (1.2 mmol) of ethyl bromopropionate, 0.21 g (1.5 mmol) of powdery anhydrous potassium carbonate, 0.017 g (0.1 mmol) of potassium iodide, and 3 ml of dry acetonitrile is allowed to react at room temperature for 5 hours and concentrated in vacuo. The crude residue is extracted with methylene chloride, and the material soluble in the methylene chloride is purified by silica gel chromatography to give the compound [12] as an oily product. For the purpose of cyclization, this is dissolved in 10 ml dry benzene containing 0.009 g (0.05 mmol) of toluenesulfonic acid (anhydrous) and refluxed azeotropically under heating for an hour in a vessel equipped with a water-separator in which 3A-Molecular sieves are placed. The reaction mixture is washed with an aqueous solution of sodium hydrogencarbonate, concentrated in vacuo, and purified by silica gel chromatography to give 0.32 g (yield 72%) of the compound [13].

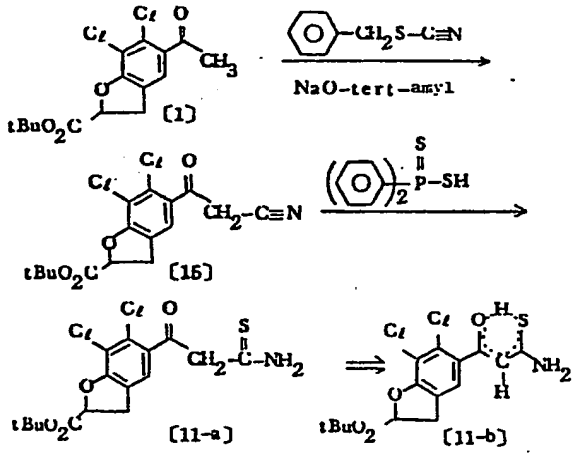
IR νmax ($CHCl_3$): 1741, 1701, 1583, 1545 cm^{-1}.
NMR δppm ($CDCl_3$): 12.55 (1H, br), 7.23 (1H, s), 5.87 (1H, s), 5.22 (1H, d-d), 3.8–2.8 (6H, m), 1.48 (9H, s).

STEP 2

A mixture of 0.3 g of the compound [13] and 3 ml of trifluoroacetic acid is stirred at room temperature for 1 hour and then treated in the same manner as in STEP 2 of Example 55 to give 0.235 g (yield 92.5%) of the titled compound [14], which is recrystallized from ethanol to give crystals, m.p. 226–228°C.

Anal. Calcd. (%) for $C_{15}H_{11}Cl_2O_5NS$: C, 46.41; H, 2.86; Cl, 18.26; N, 3.61; S, 8.26. Found (%): C, 46.19; H, 3.02; Cl, 18.32; N, 3.52; S, 8.12.
IR νmax (Nujol): 3300–2300 (br), 1747, 1642, 1595, 1561 cm^{-1}.
NMR δppm (DMSO,d-6): 12.45 (br)+11.02 (1H, keto+enol), 7.4+7.26 (1H, s), 0.63+0.6 (1H, s), 5.45 (1H, m), 3.8–2.8 (6H, m).

The starting material, t-butyl-6,7-dichloro-5-[(thiocarbamoyl)acetyl]-2,3-dihydro-benzofuran-2-carboxylate [11] can be produced in the following manner.



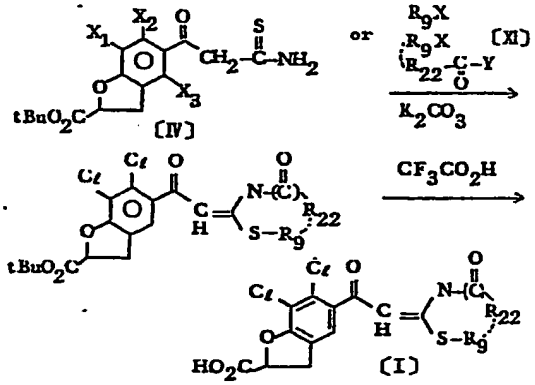
A solution of 3.03 g (10 mmol) of t-butyl 6,7-dichloro-5-acetyl-2,3-dihydro-benzofuran-2-carboxylate [1] in 5 ml of benzene is added under ice-cooling to a solution of sodium tert-amylate which is prepared by refluxing 0.48 g (12 mmol) of 60% oily sodium hydride, 1.06 g (12 mmol) of tert-amyl alcohol, and 25 ml of dry benzene, and the mixture is stirred for 0.5 hour. A solution of 2.24 g (15 mmol) of benzyl thiocyanate in 10 ml of benzene is added thereto under ice-cooling. The reaction mixture is allowed to react at room temperture overnight, to which an aqueous solution of ammonium chloride is then added. The benzene layer is separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a residue, which is purified by silica gel chromatography to give 1.08 g (yield 30.3%) of the compound [15]. This is recrystallized from a small amount of isopropyl ether to give crystals, m.p. 73–74°C.

IR νmax ($CHCl_3$): 2260 (CN), 1750, 1700, 1605 cm^{-1}.
NMR δppm ($CDCl_3$): 7.46 (1H, s), 5.30 (1H, d-d), 4.17 (2H, s), 3.85–3.24 (2H, m), 1.50 (9H, s).

A mixture of 1.21 g (3.39 mmol) of the compound [15] with 1.87 g (7.46 mmol) of diphenyldithiosulfonic acid (prepared from benzene and phosphorus pentasulfide in the same manner as in W. A. Higgins *et al.*, J. Am. Chem. Soc., *77*, 1867 (1955)) and 50 ml of isopropanol is allowed to react at 40°C overnight. The precipitating crystals are removed by filtration under ice-cooling and the filrate is concentrated in vacuo to give a residue, which is purified by silica gel chromatography to give 1.1 g (yield 83.1 %) of resinous objective compound [11] (the compound is in a mixture of keto- and enol-form in a solution.).

IR νmax ($CHCl_3$): 3560, 3500, 3385, 2540, 1748, 1603 cm^{-1}.
NMR δppm ($CDCl_3$): [enol-form: 14.54 (s), 6.70 (br), 5.76 (s)], [keto-form: 8.45, 7.8 (bs), 4.39 (s)], 7.27 (1H, m), 5.76 (1H, m), 3.8–3.2 (2H, m), 1.49 (9H, s).

Example 73–77

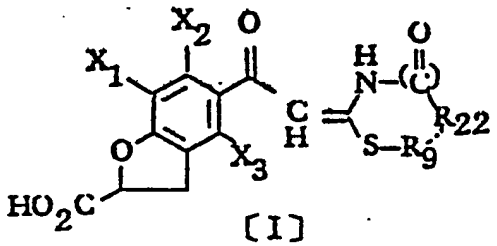


A solution of the compounds (IV) and (X I) dissolved in acetonitrile is allowed to react in the presence of anhydrous potassium carbonate. After filtration, the filtrate is concentrated in vacuo to give a residue, which is purified by silical gel chromatography. In Example 77, the reaction is carried out in benzene under refluxing in the presence of a catalytic amount of p-toluenesulfonic acid, and the reaction product is washed with sodium hydrogencarbonate, concentrated in vacuo, and then worked up in the same manner as above. The obtained compound (II) is allowed to react with a ten-fold amount of trifluoroacetic acid at room temperature for an hour, the mixture is concentrated in vacuo to give a residue, which is recrystallized from ether to give the objective compound (I).

This may be purified by recrystallization, if necessay.

Examples are more specifically explained in Table 6 (Nos. 1–4).

Table 6 (No. 1)



[I]

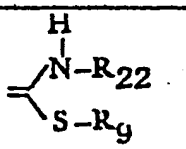
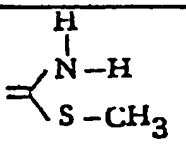
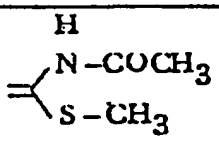
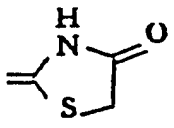
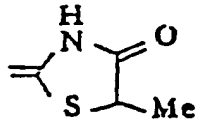
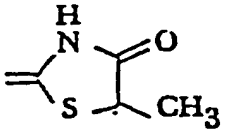
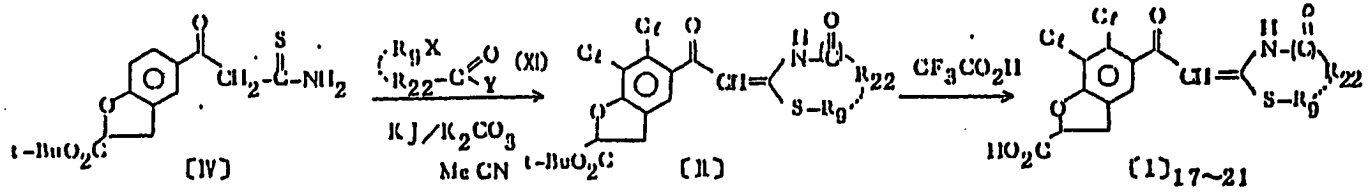
Example Nos.	X_1~X_3		Yield (%) from (IV)
73	6,7-dichloro		72.3
74	〃		38.9
75	〃		44.2
76	〃		31.5
77	〃		46.3

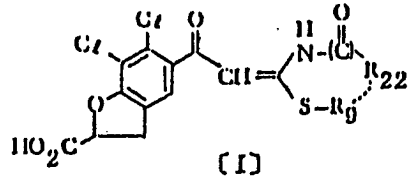
Table6 (No. 2)



Example Nos.	Amount Used g (mmol) (IV)	(XI) $\begin{matrix}R_9X\\ R_{22}-C\overset{O}{<}_{Y}\end{matrix}$	K_2CO_3	CH_3CN	Reaction Temp.	Time (hr)	[II] Yield (%)	[I] Yield (%)
73	0.16 (0.41)	CH_3J 0.07 (0.5)	0.085 (0.62)	3 ml	rt	1.0	96.4	75.0
74		CH_3J (2) (0.07) (1) (0.5) CH_3COCl 0.32 (4.1)	0.85 (6.2)	3 ml	rt	16	66.7	58.3
75	0.14 (1.025)	$BrCH_2COOMe$ 0.188 (1.23)	0.212 (1.54)	3 ml	rt	3	88.4	60.0
76	0.50 (1.28)	$Br-\underset{CH_3}{\underset{\vert}{CH}}COOC_2H_5$ 0.28 (1.54)	0.265 (1.92)	4 ml	rt	2	92.0	34.2
77	0.60 (1.54)	$Br-CH_2-\underset{CH_3}{\underset{\vert}{CH}}-CO_2C_2H_5$ -a) 0.36 (1.85)	(1) 0.32 (0.23) (2) TsOH 0.0065 g/benzene 12 ml refluxed for 1.5 hours	5 ml	rt	16	84.2	55.0

-a) which is prepared according to the method disclosed in Pickard, JACS 62 14 (1947)

Table 6 (No. 3)



[I]

Example Nos.	Recrystal from	m.p. (℃)	Molecular formula	Elementary Analysis									
				Calcd. (%)					Found (%)				
				C	H	Cℓ	N	S	C	H	Cℓ	N	S
73	ethanol	254~257(d)	$C_{14}H_{11}Cℓ_2NO_4S$	44.84	3.18	20.36	4.02	9.21	44.67	3.26	20.19	3.97	9.09
74	ethanol	217~220(d)	$C_{15}H_{13}Cℓ_2NO_5S$	46.17	3.36	18.17	3.59	8.21	46.01	3.49	18.14	3.61	8.07
75	ethanol	242~258(d)	$C_{14}H_9Cℓ_2NO_5S$	44.94	2.42	18.95	3.74	8.57	44.83	2.58	19.18	3.66	8.47
76	ethyl acetate	202~206	$C_{15}H_{11}Cℓ_2NO_5S$	46.41	2.86	18.26	3.61	8.26	46.18	2.98	18.11	3.66	8.14
77	ethanol	213~217	$C_{16}H_{13}Cℓ_2NO_5S$	47.78	3.26	17.63	3.48	7.97	47.50	3.25	17.50	3.46	7.48

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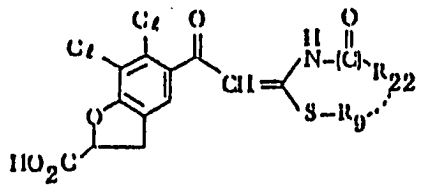
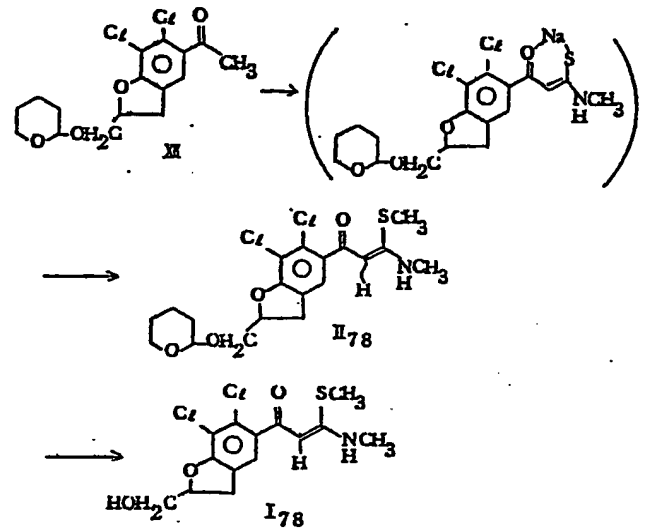
Table 6 (No. 4)



Example Nos.	IR (ν_{max}^{Nujol} cm^{-1})	NMR (δ_{ppm}^{DMSO} d-6)
73	3410, 3240, 1900(br), 1730, 1596, 1494	1.0~7.5 (2H, br) 7.26 (1H, s) 5.42 (1H, d-d) 5.23 (1H, s) 3.8~3.2 (2H, m) 2.40 (3H, s)
74	3000~2000(br), 1748, 1665, 1565(br)	13.30 (1H, s (br)) 7.46 (1H, s) 5.76 (1H, s) 5.45 (1H, d-d) 3.8~3.25 (2H, m) 2.35 (3H, s) 2.20 (3H, s)
75	3120, 3080, 1760, 1690, 1623, 1601, 1510	11.85 (1H, br) 7.32 (1H, s) 6.33 (1H, s) 5.45 (1H, d-d) 3.80~3.20 (4H, s+m)
76	3280, 1730, 1630, 1620, 1570, 1525	(※) d-6 acetone 10.5 (1H, br) 7.39+7.33 (1H, s) 6.50+6.04 (1H, s) 5.48 (1H, d-d) 4.3~3.25 (3H, m) 1.55 (3H, d)
77	3300~2300(br), 1755, 1720, 1561, 1515	12.46+11.0 (1H, br) 7.40+7.27 (1H, s) 6.30+5.86 (1H, s) 5.46 (1H, m) 3.85~2.70 (5H, m) 1.2 (m, 3H)

Example 78

6,7-Dichloro-5-[3-methylamino-3-(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-yl-methanol



A mixture of 1.0 g (2.9 mmol) of the compound X II (Example 44) and 0.112 g (3.0 mmol) of 65% sodium hydride is allowed to react for 2/3 hour in 5 ml of N,N-dimethylformamide while being stirred under nitrogen atmosphere, then combined with 0.233 g (3.2 mmol) of methyl isothiocyanate, and reacted for 2 hours. To the mixture is added 0.5 g (3.5 mmol) of methyl iodide, and reacted for further 14 hours. The reaction product is treated with n-hexane to give crude crystals, which are recrystallized from ethyl acetate to give 0.42 g (yield 33.6%) of pale yellow crystals, m.p. 176–177°C.

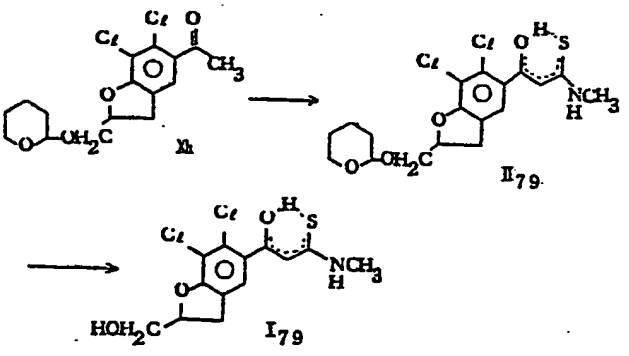
NMR δppm ($CDCl_3$): 1.63 (6H, br), 2.38 (3H, s), 2.95–4.13 (9H, m), 4.65 (1H, br), 4.83–5.40 (1H, m), 7.10 (1H), 11.38 (1H, br).

A mixture of 0.42 g (1.0 mmol) of the compound II_{78} with 5 ml of trifloroacetic acid is allowed to react at room temperature for 0.5 hour. The reaction product is chromatographed on a Lober column with an ethyl acetate/dichloromethane mixture (95:5) as eluent to give 0.24 g (yield 70.8%) of the compound I_{78}, m.p. 170–173°C. This is recrystallized from ethyl acetate to give 0.185 g (yield 54.6%) of pale yellowish crystals, m.p. 170–173°C

Anal. Calcd. (%) for $C_{14}H_{15}Cl_2NO_3S_2$: C, 48.28; H, 4.34; Cl, 20.36; N, 4.02; S, 9.21. Found (%): C, 48.09; H, 4.34; Cl, 20.09; N, 4.16; S, 8.92.
IR νmax (Nujol): 3350, 3140, 1602, 1565 cm^{-1}.
NMR δppm (DMSO, d-6): 2.42 (s), 2.73–3.43 (5H, m), 3.50–3.82 (2H, m), 4.73–5.17 (2H, m), 5.22 (1H, s), 7.25 (1H), 11.2 (1H, br).

Example 79

6,7-Dichloro-5-[3-mercapt-3-(methylamino)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-yl-methanol



The same procedure as in Example 78 is applied to this example, using 0.5 g (1.4 mmol) of

the compound X II (Example 44), 0.056 g (1.5 mmol) of 65% sodium hydride, 0.116g (1.6 mmol) of methyl isothiocyanate, and 4 ml of N,N-dimethylformamide. Then the reaction produce is chromatographed on a Lober column (type B) with an ethyl acetate/dichloromethane mixture (3:97) as an eluent to give 0.26 g (yield 42.9%) of the compound II_{79}.

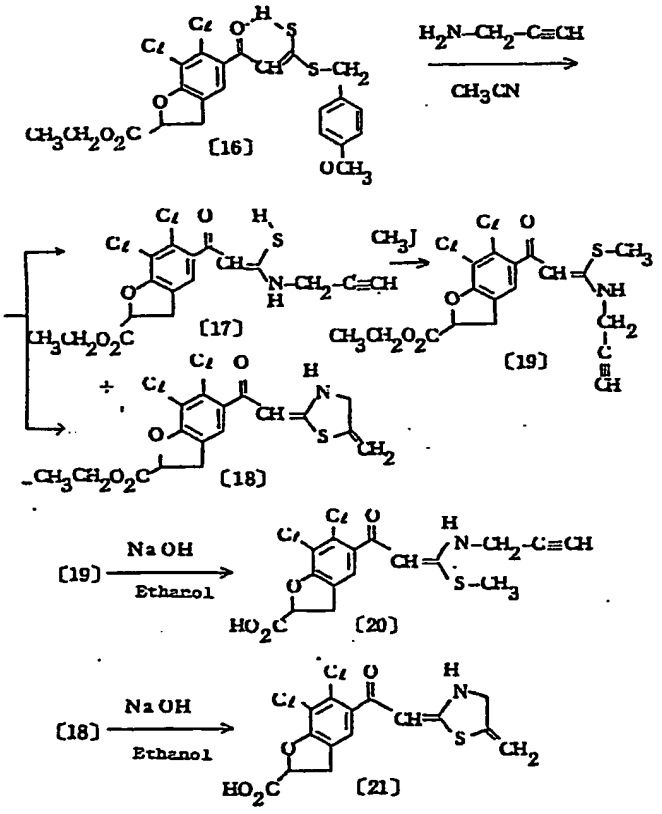
NMR δppm ($CDCl_3$): 1.58 (6H, br), 3.07–4.15 (9H, m), 4.60 (1H, br), 4.83–5.33 (1H, m), 4.35 (1H, s), 7.15 (1H).

The product which is prepared by treating 0.25 g (0.6 mmol) of the compound II_{79} in the same manner as in Example 79 is crystallized from ether to give the compound I_{79}, m.p. 121–125°C. This is recrystallized from ether to give 0.022 g (yield 2.9%) of pale yellowish crystals, m.p. 126–127°C.

Anal. Calcd. (%) for $C_{13}H_{13}Cl_2NO_3S$ $1/3(C_2H_5)_2O$: C, 47.96; H, 4.59; Cl, 19.75; N, 3.90; S, 8.93.
Found (%): C, 48.17; H, 4.37; Cl, 19.66; N. 3.85; S. 8.64.
IR νmax (Nujol): 3590, 3245, 3360, 1616, 1606 cm^{-1}
NMR δppm (Me_2CO, d-6): 1.13 (t), 2.08 (1H, br), 2.67–3.50 (5H, m), 3.63–4.20 (2H, m), 4.70–5.30 (1H, m), 5.77 (1H, s), 7.22 (1H).

Example 80

Production of 6,7-dichloro-5-[3-(methylthio)-3-propargylamino-2-propenoyl]-2,3-dihydro-benzofuran-2-carboxylic acid and 6,7-dichloro-5-[(5-methylene-thiazolidin-2-ylidene)acetyl-2,3-dihydro-benzofuran-2-carboxylic acid [21]



A solution of 0.93 g (1.86 mmol) of ethyl 6,7-dichloro-5-[3-(4-methoxybenzylthio)-3-mercapto-2-propenoyl]-2,3-dihydrobenzofuran-2-carboxylate [16] (see, Example 35) and 0.113 g (2.05 mmol) of propargylamine dissolved in 2.3 ml of dry acetonitrile is allowed to react at room temperature overnight. The compound [18] precipitated as crystals are collected by filtration and washed with a small amount of ether to give 0.195 g of the compound [18], m.p. 135–136°C. The filtrate and the ether layer are combined and concentrated in vacuo to give a residue, to which 0.35 g of powdery anhydrous potassium carbonate, 0.317 g of methyl iodide, and 5 ml of dry acetonitrile are added, and the mixture is reacted at room temperature for 2 hours. The reaction mixture is cencentrated in vacuo, and the residue extracted with dichloromethane, and

purified by silica gel chromatography to give 0.105 g (total yield 0.3 g: 40.3%) of the compound [18] and 0.08 g (yield 10.7%) of the compound [19], m.p. 151–154°C.

IR νmax ($CHCl_3$): 3310 (–CCH), 1753, 1735, 1608, 1550 (br) cm^{-1}.
NMR δppm ($CDCl_3$): 11.50 (1H, br), 7.22 (1H, s-like), 5.34, 5.30 (2H, s, d-d), 4.27, 4.18 (4H, q+m), 3.8–3.25 (2H, m), 2.42, 2.35 (4H, s+m), 1.30 (3H, t).

A solution of 0.15 g of the compound [19] dissolved in 3 ml of a dichloroethane/ethanol (1:1) mixture is treated with 0.56 ml of 1N-sodium hydroxide for an hour for hydrolysis. The reaction mixture is concentrated in vacuo, neutralized with 1N-hydrochloric acid to precipitate crystals, which are collected by filtration and washed with a small amount of ethanol to give 0.08 g of the titled compound [20]. This is recrystallized from ethanol to give 0.07 g (yield 45.6%: 4.9% from [16]) of crystals, m.p. 202–204°C (dec.).

Anal. Calcd. (%) for $C_{16}H_{13}Cl_2NO_4S$ $1/2C_2H_5OH$: C, 48.93; H, 3.87; Cl, 16.99; N, 3.36; S, 7.68. Found (%): C, 49.15; H, 4.06; Cl, 16.76; N, 3.41; S, 7.66.
IR νmax ($CHCl_3$): 3300, 3260, 1744, 1610(br), 1550(br) cm^{-1}.
NMR δppm (DMSO, d-6): 11.27 (1H, t-br), 7.30 (1H, s), 5.5–5.27 (2H, s+d-d), 4.20 (2H, d-d), 3.8–3.2 (2H, m), 2.48–2.40 (4H, m+s).

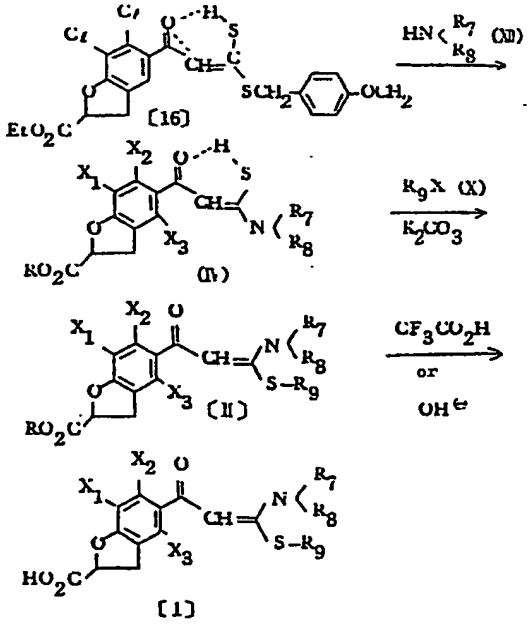
On the other hand, the compound [18] is recrystallized from benzene to give crystals, m.p. 135–136°C.

Anal. Calcd. (%) for $C_{17}H_{15}Cl_2NO_4S$: C, 51.01; H, 3.78; Cl, 17.71; N, 3.50; S, 8.01. Found (%): C, 50.81; H, 3.73; Cl, 17.93: N, 3.48; S, 8.29.
IR νmax (Nujol): 3200 (br), 1755, 1735, 1591, 1523 cm^{-1}.
NMR δppm ($CDCl_3$): 10.40 (1H, br), 7.20 (1H, s), 5.50 (1H, s), 5.4–5.2 (3H, m), 4.64 (2H, t-like), 4.26 (2H, q), 3.8–3.2 (2H, m), 1.29 (3H, t).

In the same manner as on the compound [19], 0.2 g of the compound [18] is hydrolyzed to give 0.137 g of the titled compound [21], m.p 141–143°C. This is recrystallized from ethanol/water to give 0.095 g (yield 48.7%; 19.6% from [16]) of crystals, m.p. 145–147°C.

Anal. Calcd. (%) for $C_{15}H_{11}Cl_2NO_4S$ H_2O: C, 46.16; H, 3.35; Cl, 18.17; N, 3.59; S, 8.21. Found (%): C, 46.36; H, 3.48; Cl, 18.38; N, 3.78; S, 8.27.
IR νmax (Nujol): 3570, 3200, 3000–1800 (br), 1715, 1590cm^{-1}
NMR δppm (DMSO d-6) as a mixture of keto and enol forms: 8.75 (br), 7.23 (1H, br), 5.76 (s), 5.5–5.25 (3H, m), 4.63 (m), 4.37 (2H, m), 3.85–3.2 (2H, m).

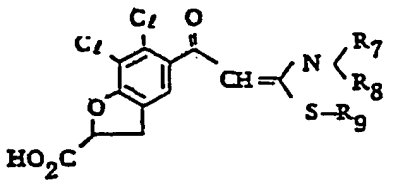
Example 81–82



The compound [16] are reacted with an amine (X II) at room temperature in acetonitrile. The reaction mixture is concentrated in vacuo, chromatographed on silica gel to give the compound (IV), to which 1.5 eq. of powdery potassium carbonate and 1.2 eq. of R_8X (X) are added, and the mixture is kept at room temperature in acetonitrile, then concentrated in vacuo to give a residue, which is purified by silica gel chromatography to give the compound (II). The compound (II) is hydrolyzed with sodium hydroxide and then neutralized with a dilute hydrochloric acid to precipitate the objective compound (I) as crystals, which is collected by filtration and purified by recrystallization.

Some examples carried out in the manner as mentioned above are shown in Table 7 (Nos. 1–4).

Table 7 (No. 1)



[I]81~82

Example Nos.	$N<^{R_7}_{R_8}$	R_9	Yield (%) from [16]
81	$-N<^{Me}_{Me}$	CH_3	18.1
82	$-N<^{H}_{CH_2-CH=CH-CH_3}$	CH_3	27.3

Table 7 (No. 2)

Exa Nos	Amount Used g (mmol) 16	[XI]	Reaction Temp. Time	Yield (%) [IV] R_9X	Reaction Temp. Time	Yield (II)
81	0.51 (1.024)	$HN<^{Me}_{Me}$ 0.07 (1.54)	r.t. 18	39.0 [CH_3I]	rt 2	~100
82	0.705 (1.41)	$H_2-CH_2-CH=CH-CH_3$ 0.12 (1.7)	13~25℃ 20	58.7 CH_3I	rt 2	95.6

Table 7 (No. 3)

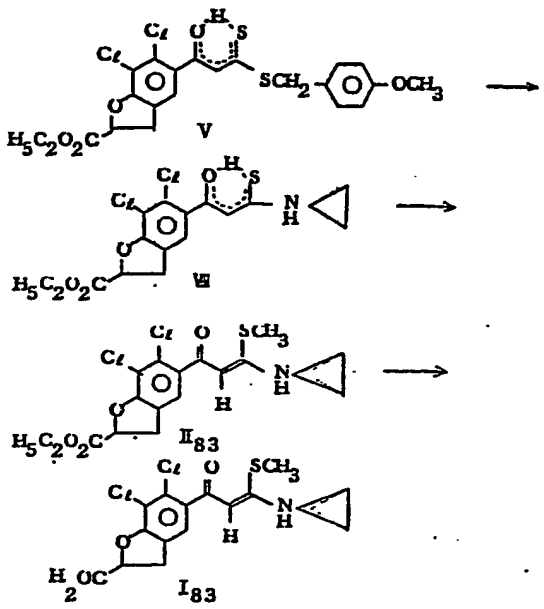
Ex. No.	Yield (%) [I]—[II]	[I] m.p. (℃)	Re-crystal from	Molecular formula	Anal. : Calcd./Found C	H	Cℓ	N	S
81	46.5	230~232(d)	ethanol	$C_{15}H_{15}Cℓ_2NO_4S$	47.88 47.64	4.02 4.02	18.85 18.81	3.72 3.69	8.52 8.21
82	48.7	213~216	ethanol	$C_{19}H_{21}Cℓ_2NO_4S$	50.76 50.71	4.26 4.28	17.63 17.75	3.48 3.49	7.97 7.74

Table 7 (No. 4)

Exa. Nos.	IR (ν_{max}^{Nujol} cm^{-1})	NMR (δ ppm $DMSO_{d-6}$)
81	~2500~(br) ~1900(br) 1730(br).1610.1560	7.22(1H.s) 5.40(1H.d-d) 5.14(1H.s) 3.8~3.1(8H.m+s) 2.40(3H.s)
82	3200~2100.2000~1800 1739.1610.1575.1564	11.35(1H.br) 7.30(1H.s) 5.8~5.22(4H.m) 3.9~3.2(4H.m) 2.40(3H.s) 1.67(3H.s)

Example 83

6,7-Dichloro-5-[3-cyclopropylamino-3-(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid



To 0.39 g (0.8 mmol) of the compound V (Example 35) are added 0.134 g (2.3 mmol) of cyclopropylamine and 2 ml of acetonitrile, and the mixture is allowed to react for 5 hours while being stirred at room temperature. The reaction product is applied to high performance liquid chromatograph on Lober column (type B) with a benzene/ethyl acetate mixture (10:1) as an eluent to give 0.23 g (yield 73.0%) of the compound VIII as a pale yellow oil.

IR νmax ($CHCl_3$): 3430, 3330, 1750, 1770 (sh), 1610 cm^{-1}.

A mixture of 0.26 g (0.6 mmol) of the compound VIII, 0.179 g (1.3 mmol) of dry powdery potassium carbonate, 0.14 g (1.0 mmol) of methyl iodide, and 4 ml of acetonitrile is reacted for an hour while being stirred at room temperature. The reaction product is subjected to liquid chromatography on a Lober column (type A) with a dichloromethane/ethyl acetate mixture (49:1) as an eluent to give 0.238 g (yield 88.5%) of the compound II_{83} as a pale yellowish oil.

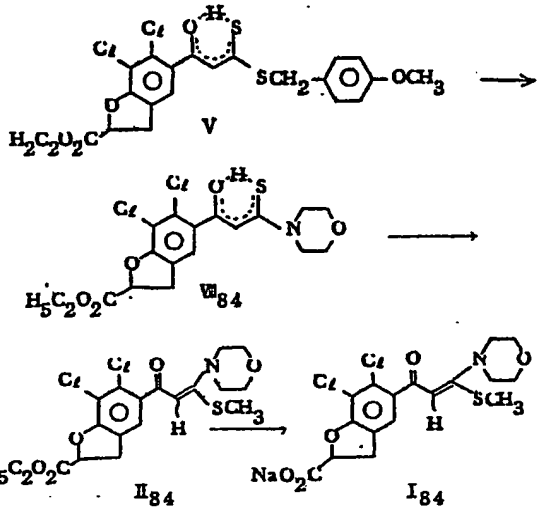
IR νmax ($CHCl_3$): 3420, 1745, 1760 (sh), 1608, 1575, 1540 cm^{-1}.
NMR δppm ($CDCl_3$): 0.60–1.07 (4H, m), 1.32 (3H, t), 2.37 (3H, s), 2.40 (1H, bro), 3.03–3.77 (2H, m), 4.25 (2H, q), 5.13–5.47 (2H, m), 7.13 (1H).

In the same manner as in the above-mentioned Example 0.230 g (0.6 mmol) of the compound II_{83} is hydrolyzed to give 0.207 g (yield 96.3%) of the compound I_{83}, m.p. 240–245°C (dec.). This is recrystallized from a acetone/ethyl acetate mixture to give 0.20 g (yield 93.0%) of grayish white crystals, m.p. 242–246°C (dec.).

Anal. Calcd. (%) for $C_{16}H_{15}Cl_2NO_4S$: C, 49.44; H, 3.89; Cl, 18.26; N, 3.61; S, 8.26 Found (%): C, 49.26; H, 3.96; Cl, 18.15; N, 3.66; S, 8.20.
IR νmax (Nujol): 3130, 2690, 2580, 2490, 1732, 1608 cm^{-1}

Example 84

6,7-Dichloro-5-[3-morpholino-3-(methylthio)-2-propenoyl]-2,3-dihydro-1-benzofuran-2-carboxylic acid



In the same manner as in Example 83, 0.29 g (0.6 mmol) of the compound V (Example 35) and 3 ml of morpholine are treated to give 0.22 g (yield 84.6%) of the compound $VIII_{84}$ as an oil.

NMR δppm ($CDCl_3$): 1.30 (3H, t), 3.13–4.53 (12H, m), 4.67 (2/3H, s), 5.17–5.58 (1H, m), 5.88 (1/3H, s), 7.25, 7.50 (1H), 15.02 (2/3H, s).

In the same manner as in Example 83 are treated 0.22 g (0.5 mmol) of the compound $VIII_{84}$, 0.136 g (1.0 mmol) of powdery potassium carbonate, 0.14 g (1.0 mmol) of methyl iodide, and 2.4 ml of acetonitrile to give 0.225 g (yield 86.5%) of the compound II_{84} as an oil.

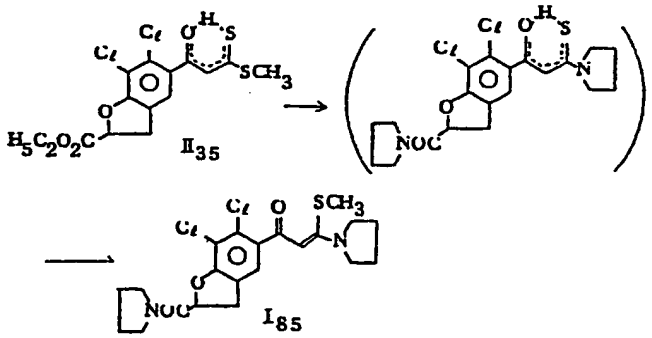
NMR δppm ($CDCl_3$): 1.30 (3H, t), 2.40 (3H, s), 3.10–3.93 (10H, m), 4.23 (2H, q), 5.12–5.45 (2H, m), 7.15 (1H).

In the same manner as in Example 83, 0.210 g (0.5 mmol) of the compound II_{84} is hydrolyzed to give 0.150 g (yield 75.8%) of the compound I, m.p. 215–216°C (dec.). This is reacted with 13.86 mg of sodium hydroxide in 3.3 ml of water for 30 minutes, and insoluble substances are removed by filtration (twice). The filtrate is evaporated to dryness, then treated with ethyl acetate, and recrystallized from an ethanol/ethyl acetate mixture to give 0.140 g (yield 66.4%) of grayish white crystals, m.p. 230–232°C (dec.).

Anal. Calcd. (%) for $C_{17}H_{16}Cl_2NO_5S_2Na$ 1/2H_2O: C, 45.44; H, 3.81; Cl, 15.78; N, 3.12; S, 7.13; H_2O, 2.00. Found (%): C, 45.47; H, 3.84; Cl, 15.88; N, 3.19; S, 7.38; H_2O, 2.12.
IR νmax (Nujol): 3300, 1621 (1615) cm^{-1}.

Example 85

6,7-Dichloro-5-[3-(methylthio-3-pyrrolidino)-2-propenoyl]-2,-3-dihydro-1-benzofuran-2-pyrrolidinamide



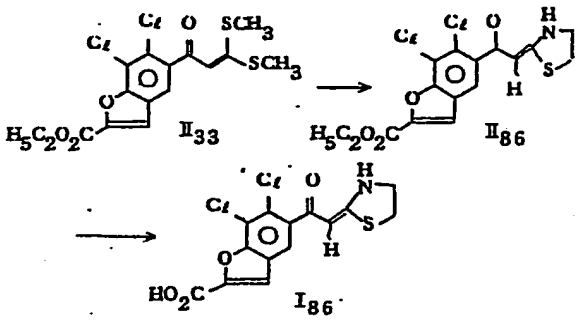
A mixture of 0.194 g (0.5 mmol) of the compound II_{35} (Example 35) with 2 ml of pyrrolidine is reacted at room temperature for an hour, then azeotropically distilled with toluene to remove an excess of pyrrolidine. To the residue are added 0.140 g (1.0 mmol) of powdery potassium

carbonate, 0.08 g (0.6 mmol) of methyl iodide, and 2 ml of N,N-dimethylformamide, and the mixture is allowed to react for an hour while being stirred at room temperature. The product is chromatographed on a Lober column (type N) with a dichloromethane/ethyl acetate mixture (9:1) as an eluent to give 0.190 g (yield 84.4%) of the compound I_{85}, m.p. 110–114°C. This is recrystallized from isopropyl ether/ethyl acetate to give 0.085 g (yield 37.8%) of compound I_{85} as grayish white crystals, m.p. 115–116°C.

Anal. Calcd. (%) for $C_{21}H_{24}Cl_2N_2O_3S$: C, 55.38; H, 5.31; Cl, 15.57; N, 6.15; S, 7.04. Found (%): C, 55.10; H, 5.15; Cl, 15.65; N, 6.11; S, 6.79.
IR νmax (Nujol): 1650, 1603, 1590 cm^{-1}.
NMR δppm ($CDCl_3$): 1.63–2.28 (8H, m), 2.47 (3H, s), 3.07–4.05 (10H, m), 5.15 (1H, s), 5.23–5.58 (1H, m), 7.20 (1H).

Example 86

6,7-Dichloro-5-[2-(1,3-thiazolidin-2-ylidene)acetyl]-1-benzofuran-2-carboxylic acid



In the same manner as in Example 19 or 34, 0.173 g (0.4 mmol) of the compound II_{33} (Example 33) is subjected to the reaction to give 0.107 g (yield 64.2%) of the compound II_{86}, m.p. 226–223°C.

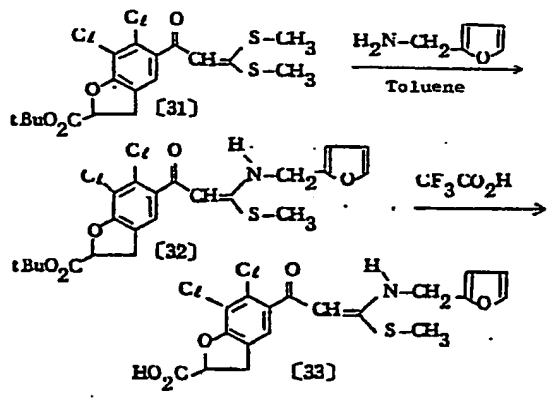
IR νmax (Nujol): 3230, 3100, 1715, 1610 cm $^{-1}$.
NMR δppm ($CDCl_3$): 1.43 (3H, t), 3.13–4.23 (4H, m), 4.43 (2H, q), 5.57 (1H, s), 7.50 (1H, s), 7.63 (1H, s).

In the same manner as in Example 33, 0.100 g (0.3 mmol) of the compound II_{86} is hydrolyzed to give 0.093 g (yield 100%) of the compound I_{86}, m.p. 265–271°C (dec). This is recrystallized from acetone to give 0.087 g (yield 87.0%) of grayish white crystals, m.p. 268–272°C (dec).

Anal. Calcd. (%) for $C_{14}H_9Cl_2NO_4S$ 1/2$(CH_3)_2CO$: C, 48.07; H, 3.12; Cl, 18.31; N, 3.62; S, 8.28. Found (%): C, 48.35; H, 3.20; Cl, 18.55; N, 3.75; S, 8.51.
IR νmax (Nujol): 3235, 2675, 2540, 2460, 1705 1612 cm $^{-1}$.

Example 87

Production of 6,7-dichloro-5-[3-(furfurylamino-3-(methylthio)-2-propenoyl]-2,3-dihydrobenzofuran-2-carboxylic acid [33]



STEP 1

A mixture of 0.435 g (1 mmol) of tert-butyl 6,7-dichloro-5-(3,3-bismethylthio-2-propenoyl)-2,3-dihydrobenzofuran-2-carboxylate [31], 0.177 g (1.2 mmol) of furfurylamine, and 1 ml of dry toluene is refluxed for 9 hours under heating. After condensation in vacuo, the residue is purified by silica gel chromatography to give 0.365 g (yield 75.3%) of the resinous compound [33].

IR νmax ($CHCl_3$): 1749 (br), 1562 (br) cm^{-1}.
NMR δppm ($CDCl_3$): 11.65 (1H, br: D_2O exchange), 7.38 (1H, m), 7.19 (1H, m), 6.31 (2H, d-like), 5.31 (s), 5.15 (m), 4.55 (2H, d), 3.73–3.15 (2H, m), 2.40 (3H, s), 1.48 (9H, s).

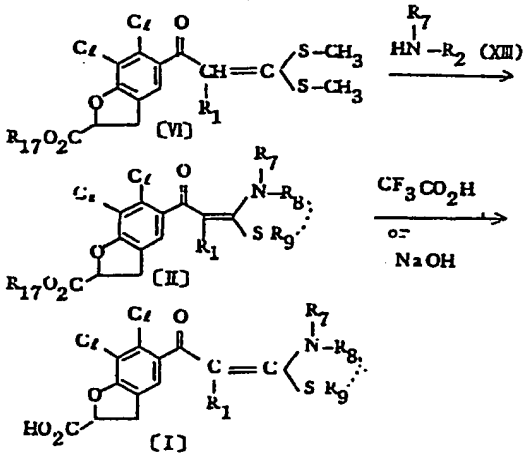
STEP 2

A mixture of 0.36 g (0.74 mmol) of the compound [32] and 3.6 ml of trifluoroacetic acid is stirred at room temperature for 0.5 hour. After condensation in vacuo, the residue is recrystallized from a small amount of ether to give 0.30 g of the titled compound [33]. This is recrystallized from ethanol to give 0.22 g of crystals (yield 69.4%; 52.3% from [31]), m.p. 214–216°C (dec.).

Anal. Calcd. (%) for $C_{18}H_{15}Cl_2NO_5S$: C, 50.48; H, 3.53; Cl, 16.55; N, 3.27; S, 7.48. Found (%): C, 50.29; H, 3.61; Cl, 16.38; N, 3.22; S, 7.39.
IR νmax (Nujol): 3200–2200(br)-1950(br), 1740, 1560 cm^{-1}.
NMR δppm (DMSO d-6): 1.53 (1H, t-br: D_2O exchange), 7.65 (1H, m), 7.31 (1H, s-like), 6.42 (2H, m) [5.42 (s)+5.15 (d) 2H], 4.10 (2H, d), 3.84–3.2 (2H, m), 2.45 (3H, s).

Anal. Calcd. (%) for $C_{15}H_{11}Cl_2NO_4S$: C, 48.40; H, 2.98; Cl, 19.05; N, 3.76; S, 8.61. Found (%): C, 48.31; H, 3:26; Cl, 18.80; N, 3.64; S, 8.47.
IR νmax (Nujol): 3365, 1752, 1602, 1585, 1570 cm^{-1}.
NMR δppm (DMSO d-6): 11.60 (1H, br), 7.23 (1H, s), 6.85 (1H, m), 6.18 (1H, m), 5.50 (1H, d-d), 3.9–3.2 (2H, m), 2.48 (3H, s).

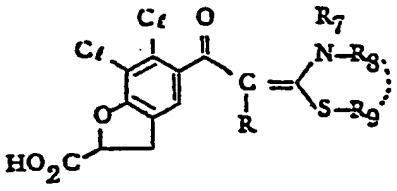
Example 88–97



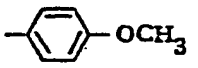
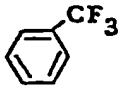
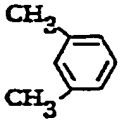
A mixture of a compound (VI) and 1.2 eq. amine compound (X III) in a solvent is refluxed under heating for 3.5 to 72 hours.

After condensation in vacuo, thus obtained residue is chromatographed on silica gel to give a compound (II), which is treated with trifluoroacetic acid (Method A) or with sodium hydroxide (Method B) for hydrolysis to give a compound (I). This is refined by recrystallization. Some examples are shown in the following Table 8 (Nos. 1–4).

Table 8 (No. 1)

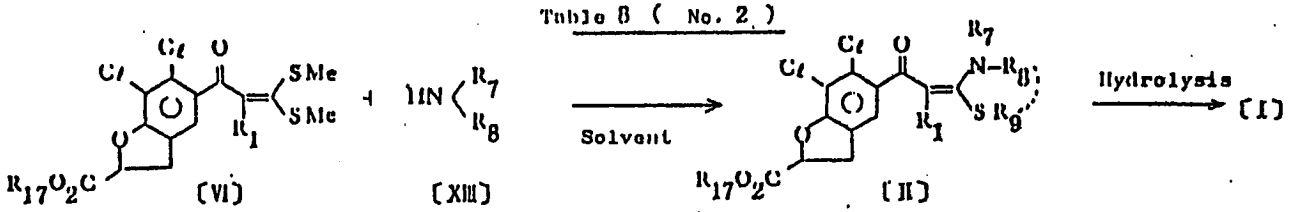


[I]$_{88\sim97}$

Example Nos.	R	R_7	R_8	R_9	Yield (%) from [VI]
88	H	H		Me	34.0
89	H	H		Me	17.6
90	H	H		Me	29 a)
91	H	H		Me	35.5
92	H	H		Me	28.9
93	H	H		Me	49.8
94	H	H	$-CH_2-CH_2-$		55.4
95	Me	H	$-CH_2-CH_2-$		22.8
96	H	Me	$-CH_2-CH_2-$		69.7
97	H	H			24.6

a) hydrolysies with NaOH (Method B)

Table 8 (No. 2)



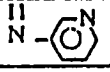
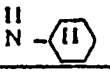
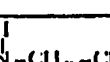
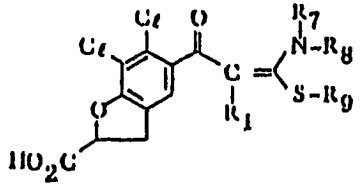
Example Nos.	Amount Used g (mmol) (IX) R_7		(X) $-N<^{R_7}_{R_8}$	Reaction Solvent(ml)	Temp.	Time	(II) Yield(%)	(I) Yield(%)
88	t-Bu	0.435(1)	$-NC_6H_4$-OMe (4)	xylene (3)	reflux temp.	3.5	70.5	48.2
89	〃		$-NC_6H_4-CF_3$ (3)	toluene (3)	〃	72	43.9	40.0
90	Et	0.53 (1.3)	$-NC_6H_3-(Me)_2$ (2.6)	xylene (3)	〃	20	40.0	72.3
91	t-Bu	0.57 (1.3)	$-NC_6H_4-F$ (2)	toluene (1.5)	〃	30	42.0	84.5
92	〃	0.485(1.1)		xylene (2.5)	〃	20	51.0	56.7
93	〃	0.52 (1.2)		xylene (3)	〃	22	93.0	53.5
94	〃	1.31 (3)	$-N-CH_2-CH_2-SH$	toluene (10)	〃	15	72.0	77.0
95	〃	2.0 (4.6)	〃	toluene (20)	〃	24	25.1	91.0
96	〃	1.0 (2.3)	$-N-CH_2-CH_2-SH$	toluene (10)	〃	16	91.0	76.6
97	〃	1.0 (2.3)		toluene (10)	〃	72	35.7	68.9

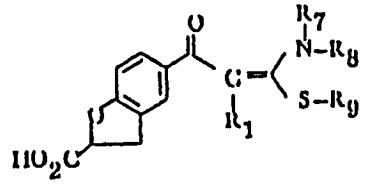
Table 6 (No. 3)



[I]88~97

Exm. Nos.	Recrystal from	m.p. (℃)	Molecular formula	Elementary Analysis									
				Calcd. (%)					Found (%)				
				C	H	Cℓ	N	S	C	H	Cℓ	N	S
88	dioxane	240~243 (d)	$C_{20}H_{17}Cℓ_2NO_5S$	52.87	3.77	15.61	3.08	7.06	52.74	3.77	15.95	2.84	7.21
89	ethanol	226~228 (d)	$C_{20}H_{14}Cℓ_2F_3NO_4S$	48.79	2.87	14.40	2.85	6.51	48.74	3.04	14.13	2.60	6.66
90	〃	252~255 (d)	$C_{21}H_{19}Cℓ_2NO_4S$	55.76	4.23	15.67	3.10	7.09	55.60	4.32	15.47	3.11	6.94
91	〃	237~242 (d)	$C_{19}H_{14}Cℓ_2NO_4S$	51.60	3.19	16.03	3.17	7.25	51.38	3.33	16.06	3.08	7.48
92	〃	227~232 (d)	$C_{18}H_{14}Cℓ_2NO_4S$	50.84	3.32	16.67	6.59	7.54	50.63	3.57	16.67	6.58	7.30
93	〃	167~168	$C_{19}H_{21}Cℓ_2NO_4S$	53.03	4.92	16.48	3.25	7.45	52.92	4.95	16.37	3.30	7.38
94	〃	252~254 (d)	$C_{14}H_{11}Cℓ_2NO_4S$	46.68	3.08	19.68	3.89	8.90	46.50	3.21	19.58	3.88	8.69
95	DMF - water	264~266 (d)	$C_{15}H_{13}Cℓ_2NO_4S$	48.13	3.50	18.95	3.74	8.57	47.99	3.64	18.89	4.00	8.26
96	DMF-ethanol	272~275 (d)	$C_{15}H_{13}Cℓ_2NO_4S$	48.14	3.50	18.95	3.74	8.57	47.93	3.57	18.55	3.79	8.45
97	〃	259~261 (d)	$C_{18}H_{11}Cℓ_2NO_4S$	52.96	2.72	17.37	3.43	7.85	52.66	2.91	17.37	3.31	7.98

Table 8 (No. 4)

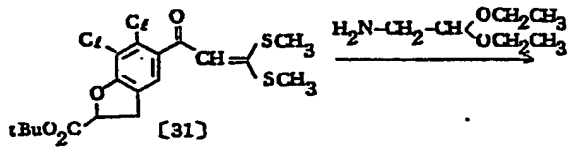


[1]88~97

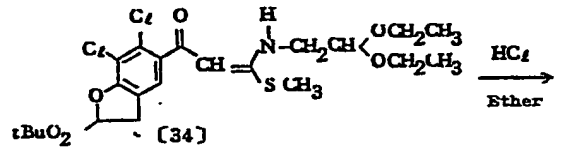
Example Nos.	IR (ν_{max}^{Nujol} cm^{-1})	NMR ($\delta_{ppm}^{DMSO_d-6}$)
88	3200~2100~1800,1737, 1610,1555,1510	12.86(1H,br) 7.39(1H) 7.25(2H,d) 6.95(2H,d) [5.48(s)+5.43(m), 2H)] 3.85~3.20(5H,m) 2.38(3H,s)
89	3200~2400,1737,1604, 1571	13.0(1H,s,br) 7.63~7.28(5H,m) 5.60(1H,s) 2.40(3H,s)
90	3200~2300(br),1775, 1733,1612,1528,1493	12.40(1H,brs) 7.43(1H,s) 7.17(3H,s) 5.49(1H,s) 5.45(1H,dd), 3.9~3.2(2H,m) 2.33(3H,s) 2.20(6H,s)
91	3200~2400(br),1743, 1618,1603,1565	12.81(1H,s;br) 7.7~7.2(5H,m) 5.61(1H,s) 2.43(3H,s)
92	3200~2450(br),1720(br) 1605~1550(br)	12.87(1H,s,br) 8.0~7.4(5H,m) 5.61(1H,s) 2.44(3H,s)
93	3200~2400(br),2000~1850 (br),1743,1608,1562	11.55(1H,d) 7.30(1H,s) 5.20(1H,s) 3.8~3.18(3H,m) 2.40(3H,s) 2.1~1.2(10H,br)
94	3240~2500(br),1730(br), 1614,1567	10.2(br)+8.55(br):1H 7.25(1H,s,br) [5.75(br)+5.3(m)]:2H 4.0~3.0(6H,m)
95	3220~2720~2400,1730, 1610,1570	10.50+7.75(br,1H) 7.01(1H,br) 5.40(1H,m) 4.0~3.0(6H,m) 1.61(3H,br)
96	~2420~(br),2000~1800, 1730(br),1609,1565	7.25(1H,s) 5.56(1H,s) 5.42(1H,m) 3.8~2.8(9H)
97	~2500(br.)~1800~(br) 1719,1688,1606	13~12(1H,br) 7.9~7.1(m,5H) 6.27(1H,s) 5.45(1H,dd) 3.85~3.2(2H,m)

Example 98

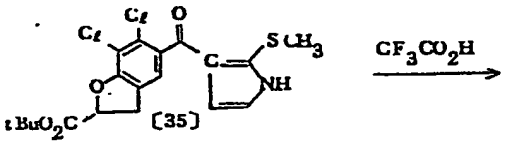
Production of 6,7-dichloro-5-[2-(methylthio)pyrrol-3-yl-carbonyl]-2,3-dihydrobenzofuran-2-carboxylic acid [36].



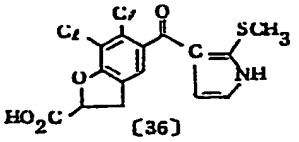
[31]



[34]



[35]



[36]

In the same manner as in Example 97, 1.09 g (2.5 mmol) of the compound [31] is reacted with 0.33 g (2.5 mmol) of 2,2-diethoxyethlamine in toluene for 16 hours to give 1.02 g (yield 80.9%) of the compound [34].

NMR δppm ($CDCl_3$): 11.45 (1H, t-like), 7.22 (1H, s), 5.30 (1H, s), 5.19 (1H, d-d), 4.69 (1H, t); 3.85–3.2 (8H, m), 2.40 (3H, s), 1.48 (9H, s), 1.26 (6H, t).

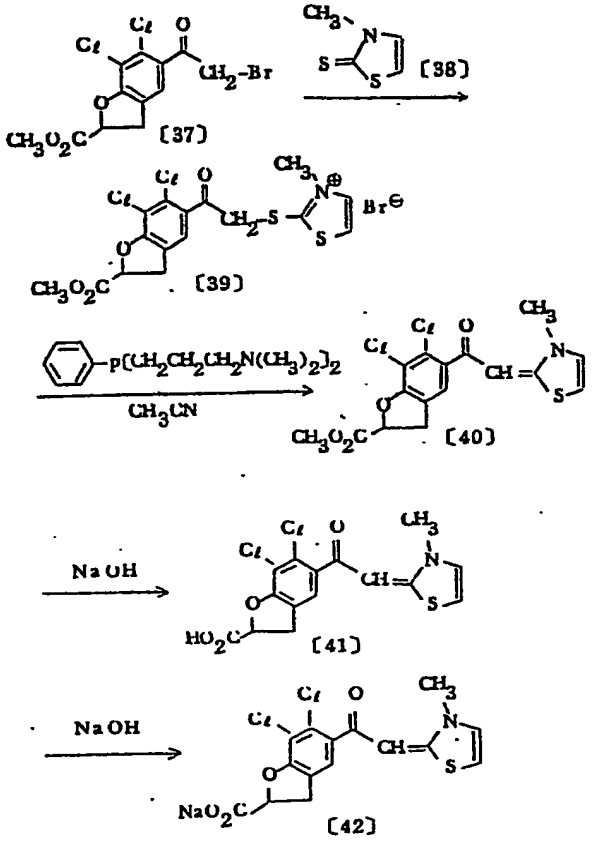
To a solution of 0.9 g (1.78 mmol) of the compound [34] in an ether (15 ml): dichloromethane (15 ml) mixture is added 8 ml (8 mmol) of 1N-hydrochloric acid in ether anhydrous, and the mixture is allowed to react at 5–25°C overnight. After condensation in vacuo, the residue is dissolved in dichloromethane, washed with an aqueous solution of sodium hydrogencarbonate, and then purified by silica gel chromatography to give 0.445 g (yield 58.2%) of the compound [35], m.p. 187–188°C.

NMR δppm ($CDCl_3$): 11.58 (1H, br), 7.20 (1H, s), 6.82 (1H, m), 6.15 (1H, m), 5.42 (1H, d-d),, 3.85–3.15 (2H, m), 2.45 (3H, s), 1.47 (9H, s).

The compound [35] (0.445 g) is allowed to react with 5 ml of trifluoroacetic acid at room temperature for 1 hour, the reaction mixture is concentrated in vacuo, crystallized from ether, washed with a small amount of 50% ethanol, and recrystallized from 95% ethanol to give 0.21 g (yield 54.3%) of the titled compound [36], m.p. 232–234°C.

Example 99

Production of 6,7-dichloro-5-[(3-methyl-4-thiazolin-2-ylidene)acetyl]-2,3-dihydrobenzofuran-2-carboxylic acid [41] and the sodium salt [42]



In 10 ml of dry acetone, 3.68 g (10 mmol) of methyl 6,7-dichloro-5-bromoacetyl-2,3-dihydrobenzofuran-2-carboxylate [37] is treated, at 40–45°C for 5 hours, with 1.31 g (10 mmol) of N-methylthioazole-2-thione [38] (prepared according to M.O. Kolosova *et al.*, J. Gen. Chem. (USSR) *33* (8), 2706 (1963)). To the reaction mixture is added 10 ml of benzene, and the precipitating crystals are collected by filtration and washed with a small amount of acetone to give 4.73 g (yield 94.8%) of the compound [39], m.p. 126–128°C.

NMR δppm (DMSO d-6): 8.42 (1H, d), 8.15 (1H, d), 7.96 (1H, s), 5.68 (1H, d-d), 5.40 (2H, s), 4.06 (s)-3.73 (s)-3.20 (8H, m).

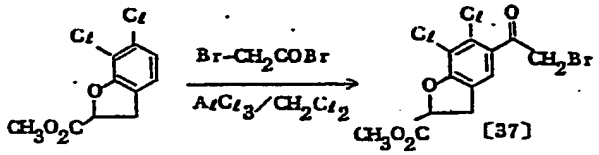
To a suspension of 1.50 g (3 mmol) of the compound [39] in 10 ml of acetonitrile is added a solution of 0.308 g (3.3 mmol) of phenyl-bis[N,N-dimethylaminopropyl]phosphine (prepared according to Loeliger P. Org. Synthesis *55*, 127 (1976)) in 1 ml of acetonitrile while being stirred under ice-cooling, and then the mixture is allowed to react for 0.5 hour while being stirred at room temperature. After condensed in vacuo, the residue is dissolved in dichloromethane, washed with 1N-sodium dihydrogenphosphate (NaH_2PO_4) solution and with water, dried over anhydrous magnesium sulfate, concentrated in vacuo, and then purified by silica gel chromatography (Lober column type B) to give 0.94 g (yield 81.1%) of an oily material, which is the methyl ester [40] of the tilted compound.

IR νmax ($CHCl_3$): 1760, 1743, 1609, 1564 cm^{-1}.
NMR δppm ($CDCl_3$): 7.31 (1H, s-like), 6.88 (1H, d), 6.48 (1H, d), 6.04 (1H, d), 3.80 (3H, s), 3.7–3.2 (5H, m+s).

To a solution of 1.2 g (2.75 mmol) of the compound [40] dissolved in 15 ml of an ethanol/dichloromethane (2/1) mixture is added 4.7 ml (4.7 ml) of 1N-sodium hydroxide, and the mixture is subjected to hydrolysis at room temperature for an hour. After condensed in vacuo, the residue is adjusted to pH 3 with dil. hydrochloric acid and acetic acid to precipitate crystals, which are collected by filtration and washed with water and with ethanol to give 1.09 g (yield 95%) of the titled compound, m.p. 280–283°C (dec.).
This is recrystallized from DMF/ethanol to give yellowish crystals, m.p. 280–283°C (dec.)

Anal. calcd. (%) for $C_{15}H_{11}Cl_2NO_4S$: C, 48.40; H, 2.98; Cl, 19.05; N, 3.76; S, 8.61. Found (%): C, 48.28; H, 3.11; Cl, 18.98; N, 3.77; S, 8.71.
IR νmax (Nujol): 3140, 3120, 2000 (br), 2000–1800, 1733, 1607, 1520 cm $^{-1}$.
NMR δppm (DMSO d-6): 7.40–7.35 (2H, m), 6.30 (1H, d), 6.00 (1H, s-like), 5.43 (1H, d-d), 3.85–3.2 (5H, m+s).

The starting material, *i.e.*, methyl 6,7-dichloro-5-(bromoacetyl)-2,3-dihydrobenzofuran-2-carboxylate [37] can be prepared according to the following reaction scheme.



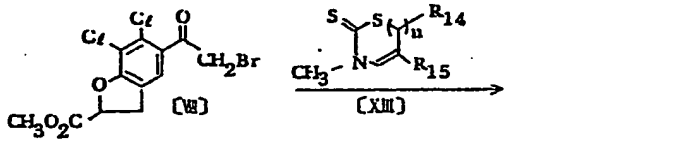
To a solution of 6.2 g (25 mmol) of methyl 6,7-dichloro-2,3-dihydrobenzofurancarboxylate (m.p. 113–114°C: prepared according to William F. Hoffman J. Med. Chem., *24* 865 (1981)) and 6.56 g (32.5 mmol) of bromoacetyl bromide dissolved in 62 ml of dry dichloromethane is added 8.6 g (65 mmol) of anhydrous aluminium chloride under ice-cooling, and then the mixture is allowed to react at room temperature for 3 hours. The reaction mixture is poured into a mixture of ice and hydrochloric acid, then extracted with dichloromethane, and washed with water. The organic layer is dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 8.5 g of crystals. This is recrystallized from benzene/cyclohexane to give 7.5 g (yield 81.5%) of the objective compound [37], m.p. 108–111°C.

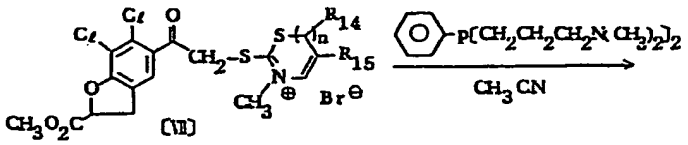
NMR δppm ($CDCl_3$): 7.35 (1H, s-like), 5.38 (1H, d-d), 4.48 (2H, s), 3.88–3.3 (5H, m+s).

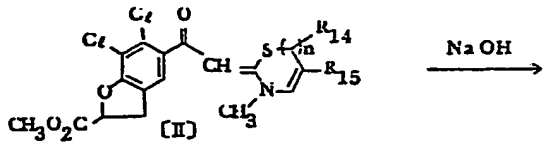
*Production of sodium salt [42]:
In 9.9 ml (99% molar ratio) of 0.1N-sodium hydroxide is dissolved 0.372 g (1 mmol) of the carboxylic acid [41]. The insoluble carboxylic acid is removed by filtration and the filtrate is concentrated in vacuo to give a residue, which is rcrystallized from a small amount of water, collected by filtration under cooling, and washed with a small amount of ethanol to give 0.255 g (63.3%) of the sodium salt [42] containing 1/2 molecule of H_2O.

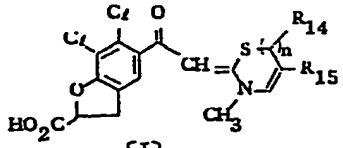
Anal. calcd. (%) for $C_{15}H_{10}Cl_2NNaO_4S$ 1/2H_2O: C, 44.68; H, 2.75; Cl, 17.59; N, 3.47; Na, 5.70; S, 7.95. Found (%): C, 44.83; H, 2.89; Cl, 17.84; N, 3.56; Na. 5.60; S, 8.17.
IR νmax (Nujol): 3400, 3150, 1622, 1568, 1492 cm $^{-1}$.

Example 100–102









STEP 1

A solution of the compound (VIII) and a compound (X III) (1.1 molar eq. each) dissolved in dichloromethane or acetone is kept at room temperature for 2–3 days while being stirred. Ether is added to the reaction mixture to precipitate crystals, which is washed with ether to give a compound (VII). This may be used for the following step without purification.

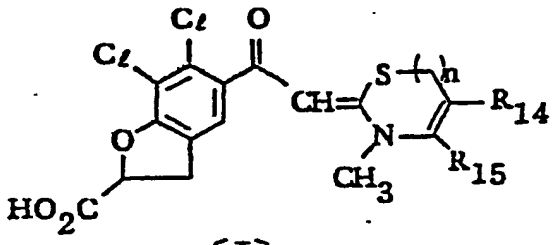
STEP 2

To a suspension of a compound (VIII) in dry acetonitrile is added 1.1 molar eq. of phenyl bis-(N,N-dimethylpropyl)phosphine, and the mixture is allowed to react at room temperature for an hour. After condensation in vacuo, the residue is dissolved in dichloromethane. The solution is washed with 1N-sodium hydrogenphosphate, then with water, dried over anhydrous magnesium sulfate, concentrated in vacuo, and purified by silica gel chromatography to give a compound (II).

STEP 3

To a solution of a compound (II) dissolved in ethanol or an ethanol/dichloromethane mixture is added 1.5 eq. of 1N-sodium hydroxide for hydrolysis at room temperature. The reaction mixture is neutralized with dil. hydrochloric acid to precipitate crystals, which are recrystallized from a proper solvent to give a compound (I). Some examples are shown in Table 9 (Nos. 1–4).

Table 9 (No. 1)



[I]101~102

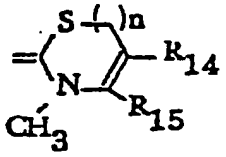
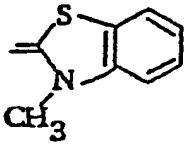
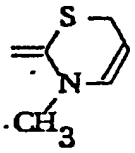
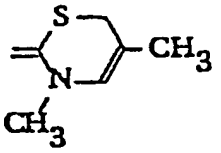
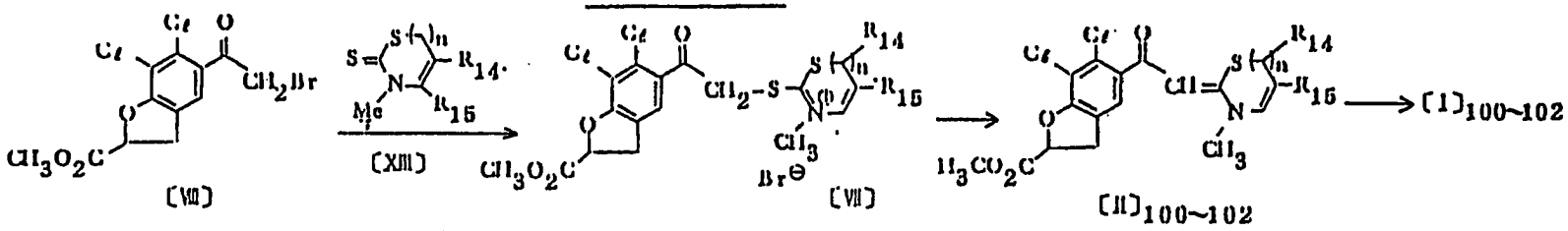
Example Nos.		Yield from [37]
100		44.2 %
101		43.2 %
102		60.4 %

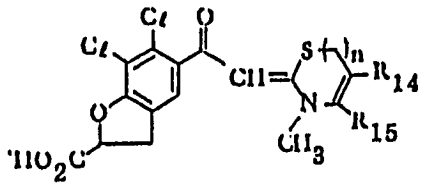
Table 9 (No. 2)



Example Nos.	Amount Used g (mmol) [VII]	[XIII]	Solvent (ml)	Temp.	Time	[VI] Yield (%)	[VI] m.p. (°C)	[II] Yield(%)	[I] Yield(%)
100	1.47 (4)	0.8 (4.4)	CH_2Cl_2	r.t.	3 Days	80.5	121~122	81.3	60.7
101	0.368 (1.0)	※-b) 0.16 (1.1)	CH_2Cl_2 (2)	r.t.	3 Days	79.8	115~117(d)	69.3	85.6
102	0.48 (1.3)	※-b) 0.23 (1.44)	acetone (3)	r.t.	2 Days	92.0	134~136	69.9	94.0

b) prepared according to the method disclosed in Garraway JCS 4004-4010 (1964)

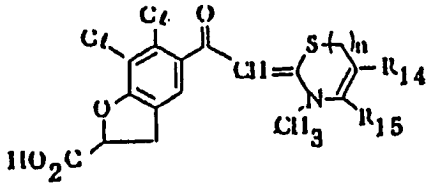
Table0 (No. 3)



[I]100~102

Example Nos.	IR (ν_{max}^{Nujol} cm^{-1})	NMR (δ_{ppm}^{DMSO} d-6)
100	~2500(br) ~1900~(br) 1747,1605,1554	7.9~7.1(5H,m) 6.30(1H,s) 5.45(1H,d-d) 3.9~3.2(5H,m+s)
101	3200~2300,~1900~(br) ~1760(br),1664,1607, ~1530(br)	7.30(1H,slike) 6.35(1H,d) 5.84(1H,s) 5.5~5.1(2H,m) 3.83~3.15(7H,m+s)
102	3200~1800(br),1730, 1604,1540	7.29(1H,slike) 6.18(1H,br) 5.77(1H,s) 3.84~3.13(7H, m+s) 1.78(3H,s)

Table 9 (No. 4)



[I]100~102

Exa. Nos.	Recrystal from	m.p. (℃)	Molecular formula	Elementary Analysis									
				Calcd. (%)					Found (%)				
				C	H	Cℓ	N	S	C	H	Cℓ	N	S
100	DMF – ethanol	283~285(d)	$C_{19}H_{13}Cℓ_2NO_4S$	54.04	3.10	16.79	3.32	7.59	53.87	3.37	16.74	3.54	7.41
101	DMF – ethanol	224~227(d)	$C_{16}H_{13}Cℓ_2NO_4S$	49.75	3.39	18.36	3.63	8.30	49.71	3.49	18.35	3.77	8.00
102	DMF – ethanol	219~221(d)	$C_{17}H_{15}Cℓ_2NO_4S$	51.01	3.78	17.71	3.50	8.01	50.80	3.89	17.69	3.58	7.91

Effect of the Invention

Compounds prepared in Examples above are evaluated by the following pharmacological test.

I. Test Method:

Experiments with rats and mice were carried out according to Assay Programs #27–104 and #27–106, respectively. The outline is as follows.

1. Bioassay for Diuretic Effect on Rats

Slc:SD 8-week-old rats (male, about 250g body-weight each) were used for the test. A few lumps of sugar in place of ordinary diets were given on the morning of the day before the test day and 5% glucose solution was given orally at a rate of 20 ml/kg in the evening (approximately at 4 p.m.) of the test day. In the morning for the test, a sample which was prepared by suspending or dissolving a test compound in 2% gum arabic was orally administered to each at a dose of 20 ml/kg. On the other hand, mere by 2% gum arabic was orally administered to the control group at 20 ml/kg. Immediately after the administration, the test animals were put in a plastic cage for the metabolic tests and their urine samples were collected for 5 hours. The cumulative urine volume, urinary sodium (Na^+), and urinary potassium (K^+) were quantitatively determined.

2. Bioassay for Diuretic Effect on Mice

Slc:ddy 5-week-old mice (female, about 20g body-weight each) were used for the test. From the morning of the day before the test day, the mice were fasted but water. In the morning of the test day, a sample which was prepared by suspending or dissolving a test compound in 2% gum arabic was orally administered to each at 30 ml/kg. On the other hand, mere by 2% gum arabic was orally administered to the control group at 30 ml/kg. Immediately after the administration, 5 mice employed were put in a plastic cage for the metabolic tests and their urine samples were collected for 4 hours. The cumulative urine volume, urinary sodium (Na^+), and urinary potassium (K^+) were quantitatively determined.

II. Test Results.

Results on some typical compounds are shown in Table 10.

Results regarding the urine volume are shown by percentages to control (100%). Also, results regarding the urinary sodium (Na^+) and the urinary potassium (K^+) are shown by percentages to control (100%). The asterisk* indicates that the compounds are recognized to be significantly effective.

Table 10

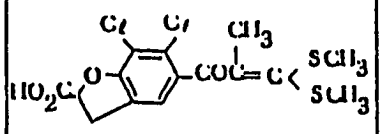
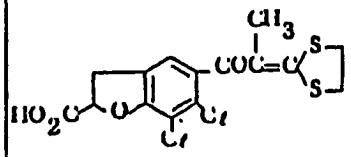
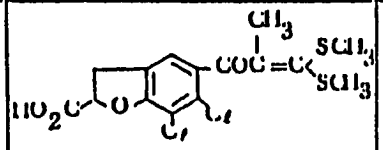
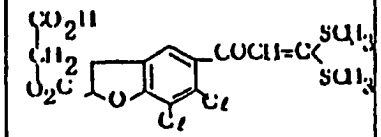
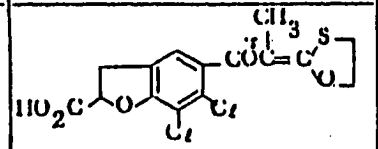
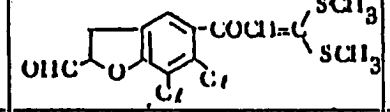
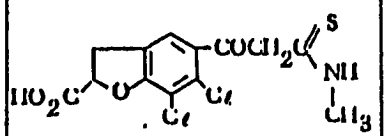
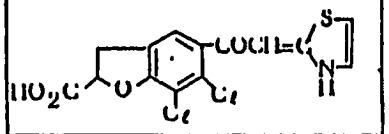
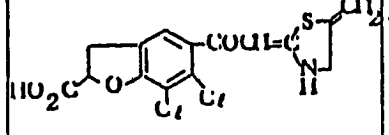
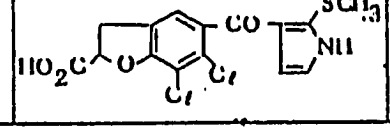
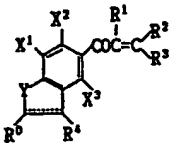
Example Nos.	Structural formula of Test Compound	Rat				Mouse			
		Dose (mg)	Urine Vol. (%)	Urinary Na^+ (%)	Urinary K^+ (%)	Dose (mg)	Urine Vol. (%)	Urinary Na^+ (%)	Urinary K^+ (%)
1		30	111	236※	143	3	117	183※	121
		50	139※	492※	236※				
		100	162※	570※	450※	30	324※	1000※	262※
3		50	153※	291※	217※	30	270※	1370※	304※
14		–	–	–	–	30	290※	743※	330※
17		50	144※	478※	285※	30	216※	970※	277※
21		50	104	179※	178※	30	155※	704※	273※

Table 10 (Continued)

Example Nos.	Structural formula of Test Compound	Rat				Mouse			
		Dose (mg)	Urine Vol. (%)	Urinary Na^+ (%)	Urinary K^+ (%)	Dose (mg)	Urine Vol. (%)	Urinary Na^+ (%)	Urinary K^+ (%)
28						30	222※	905※	260※
67		50	148※	377※	306※	30	192※	610※	232※
70		50	154※	459※	374※	30	144※	410※	178※
80		10	101	211※	161※	30	264※	738※	344※
98		10	157※	445※	254※	30	222※	810※	292※

CLAIMS

1. A compound of formula (I)

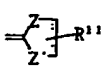
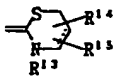
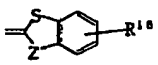


(I)

wherein X^1, X^2, and X^3 are each independently hydrogen, halogen or CH_3; Y is an oxygen or sulfur atom; R^1 is hydrogen, alkyl, alkenyl, aryl, aralkyl or akoxycarbonyl; R^2 is SR^5, OR^6 or NR^7R^8, wherein R^5 is hydrogen, alkyl, alkenyl, alkylnyl, aryl, aralkyl or carbamoylmethyl, R^6 is alkyl, R^7 and R^8 are each independently hydrogen, alkyl, alkenyl, cycloalkyl, aryl, furylmethyl or acyl or when R^7 and R^8 are considered together ewith the adjacent nitrogen atom they may form pyrrolidino, piperidino or morpholino or one of R^7 and R^8 is hydrogen and the other is $-C(O)R^{22}$ where R^{22} is alkyl, substituted alkyl, alkylene or substituted alkylene; R^3 is SR^9 or $S(O)RR^{10}$, wherein R^9 is hydrogen, alkyl, alkenyl, alkynyl or aralkyl and R^{10} is alkyl;
R^4 is hydrogen or alkyl, R^0 is CHO, $COCH_3$, $COOCH_2COOH$, CN, CH=NOH, $COOR^{17}$, CH_2OR^{18}, $CONR^{19}R^{20}$ or $CH_2OC(O)-CH_2R^{21}$, wherein R^{17} is hydrogen, alkali metal, or alkyl, R^{18} is hydrogen, alkyl or acyl, R^{19} and R^{20} are each independently hydrogen or alkyl or R^{19} and R^{20} may form pyrrolidino together with the adjacent nitrogen atom, and R^{21} is hydrogen or lower alkyl;

 may be  ; and,

may be any one of the following;

  and 

wherein Z is O, S, or NH, Z′ is S or N–R^{12}, Z″ is S, NH or N–CH_3, R^{11} is hydrogen, alkyl, alkoxy, carbonyl or methylene, R^{12}, R^{13}, R^{14} and R^{16} are each independently hydrogen or alkyl, R^{15} is hydrogen or carbonyl, and the dotted line represents the presence or absence of a double bond.

2. A compound as claimed in claim 1 and referred to hereinbefore.

3. A salt of a compound as claimed in claim 1 or claim 2.

4. A process for preparing a compound as claimed in claim 1, which process comprises effecting at least one step as presented hereinbefore in any one of Reaction Schemes 1 to 10 and which leads directly to such a compound.

5. A process for preparing a compound as claimed in claim 1 and substantially as hereinbefore described in any one of the Examples.

6. A pharmaceutical or veterinary formulation comprising a compound as claimed in claim 1 or claim 2 or a salt as claimed in claim 3, in either case formulated for pharmaceutical or veterinary use, respectively.

7. A formulation as claimed in claim 6 and in unit dosage form.

8. A formulation as claimed in claim 6 or claim 7 and also comprising an acceptable diluent, carrier or excipient.

9. A method of making a medicament for producing an antihypertensive, diuretic or uricosuric effect, which method comprises formulating a compound as claimed in claim 1 or claim 2 or a salt as claimed in claim 3 for such purpose.

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